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PHARMACOPEIAL FORUM VOL. 31 NO. 1 JAN.–FEB. 2005

* The *USP–NF* (*USP29–NF24*), 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:

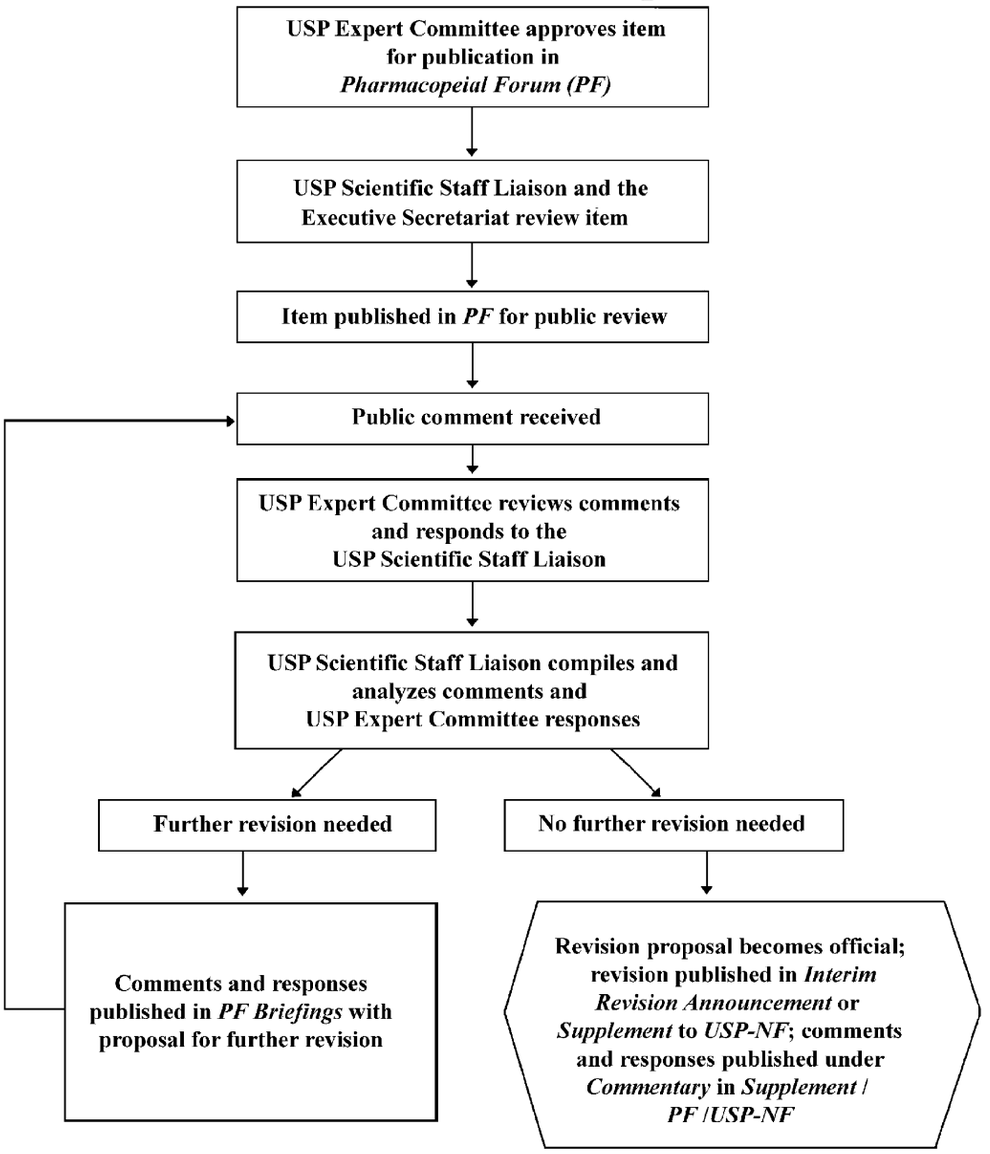
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official 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. 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* 31(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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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.

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, Scientist	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)
Shawn C. Becker, Director Patient Safety	scb@usp.org	(301) 816-8216	Safe Medication Use
Daniel K. Bempong, Scientist	dkb@usp.org	(301) 816-8143	Excipient Monograph Content (EMC)
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Barbara A. Bowman, Manager, Administrative Services	bab@usp.org	(301) 816-8278	USP Correspondence
William E. Brown, Senior Scientist	web@usp.org	(301) 816-8380	Biopharmaceutics (BPC); Biostatistics (BST)
Evelyn Bryant, Manager, Editorial Services	eb@usp.org	(301) 816-8302	
Damian A. Cairatti, Senior Scientific Associate	dac@usp.org	(301) 816-8703	USP, Spanish Edition; Bioavailability and Nutrient Absorption (BNA)
Larry N. Callahan, Scientist	lnc@usp.org	(301) 816-8385	Biotechnology and Natural Therapeutics and Diagnostics (BNT)
Todd L. Cecil, Director, Scientific Administration	tlc@usp.org	(301) 816-8234	
Roger Dabbah, Director, Complex Actives	rd@usp.org	(301) 816-8336	
Behnam Davani, Senior 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, Scientist	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

STAFF DIRECTORY *(continued)*

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Elena Gonikberg, Senior 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)
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Margareth R. Marques, Senior Scientist and Latin American Liaison	mrm@usp.org	(301) 816-8106	Biopharmaceutics (BPC); Reagents
Tina S. Morris, Senior Scientist	tsm@usp.org	(301) 816-8397	Vaccines, Virology, and Immunology (VVI)
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)
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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)
Ravi Ravichandran,Senior Scientist	rr@usp.org	(301) 816-8330	Pharmaceutical Analysis 3 (PA3); Excipient Monograph Content (EMC)
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 Monograph Content (EMC)
Jennifer Salguero, Scientist	jxs@usp.org	(301) 816-8371	Dietary Supplement Information

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Stefan P. Schuber, Director, Standards Development and Administration	sps@usp.org	(301) 816-8551	
Catherine M. Sheehan, Scientist	cxs@usp.org	(301) 816-8262	Excipient Monograph Content (EMC)
Eric B. Sheinin, Vice President, Department of Standards Development	es@usp.org	(301) 816-8103	
Radhakrishna S. Tirumalai, Scientist	rst@usp.org	(301) 816-8339	Blood & Blood Products (BBP); General Toxicology and Biocompatibility (GTB)
Andrzej Wilk, Scientist	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 SCIENTIFIC ADMINISTRATION. USP is pleased to announce that Todd L. Cecil, Ph.D., has been named as the Director, DSD Scientific Administration. As part of his duties, he will be responsible for the day-to-day operations of the DSD scientific staff. He is also responsible for ensuring that scientific information included in the compendia is complete and relevant and is responsible for providing support to *USP–NF* users. In addition, Dr. Cecil has a significant role in the development of the updated infrastructure USP requires to track the monograph development process.

Most recently, Dr. Cecil served as the DSD Director of General Policies and Requirements at USP where he was responsible for the development of general chapters.

Dr. Cecil may be reached by telephone at 301-816-8234, and via email at tlc@usp.org.

NEW DIRECTOR NAMED FOR VOLUNTEER AND ORGANIZATIONAL AFFAIRS. USP is pleased to announce that Angela G. Long has been named DSD Director, Volunteer and Organizational Affairs. As part of her duties, she will be responsible for the following: support and services for the USP Council of Experts and specifically the members of the Standards Expert Committees; Executive Secretariat support to the USP Council of Experts; organizational affairs and outreach with scientific professional, trade, and standards-setting organizations and manufacturers; management of USP Stakeholder Forums and Project Teams; serving as liaison to USP's International Quality Communication Groups; and management of USP's meetings.

Most recently, Ms. Long served as Program Director, Professional Affairs where she was involved in outreach to and communication with professional and trade organizations and USP meetings.

Ms. Long joined USP in 1990. She left briefly to operate her own communications business that focused on pharmaceutical organizations and returned to USP in 2002. Prior to joining USP in 1990, Ms. Long worked for USA TODAY.

Ms. Long may be reached by telephone at 301-816-8382, and via email at agl@usp.org.

NEW DIRECTOR NAMED FOR GENERAL POLICIES AND REQUIREMENTS. USP is pleased to announce that David A. Porter, Ph.D., has been named as the new DSD Director for General Policies and Requirements. As part of his duties, he will be responsible for the development of general chapters and monographs.

Most recently, Dr. Porter served as the DSD Associate Director of Complex Actives at USP where he was involved in activities with the Analytical Microbiology Expert Committee. Prior to joining USP, he acquired significant industrial experience in pharmaceutical and cosmetic research, development, and clinical affairs.

Dr. Porter may be reached by telephone at 301-816-8225, and via email at dap@usp.org.

ADVANCE NOTICE OF UPCOMING OFFICIAL REVISIONS TO THE *USP–NF*. In order to provide as much time as possible for industry to adopt revisions made to the compendia, upcoming official revisions to the *USP–NF* are now being announced on the USP website as soon as they are voted on to become official by the appropriate Expert Committees of the Council of Experts.

Readers are directed to the "Notices" section found in the top right corner of the USP homepage at www.usp.org. By clicking on "Upcoming Official Revisions to the *USP–NF:* Reference Standards Required But Not Available" you are taken to a page where upcoming revisions to the compendia are listed. The information posted includes the title of the item being revised, the *PF* citation where the revision was proposed, and a description of the proposal. In addition, an e-mail link to the USP Scientific Liaison for each revision is listed in parentheses after the item. The actual content and official date of each revision will be published in either an annual edition, *Supplement,* or *Interim Revision Announcement* and the items are sorted according to the publication in which they are to appear.

In addition, readers will also find a list of new USP Reference Standards that correspond to new *USP–NF* monographs but unfortunately are not yet available. The official dates of any *USP–NF* Standards, tests, or assays that require the use of these Standards are postponed until further notice pending availability of the Standards.

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 Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@usp.org, 301-816-8530; or visit the website at www.usp.org/education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2005

Date	Name of course	Location
January 11	Fundamentals of Titrations (Lecture Only)	USP Headquarters, Rockville, MD
February 3	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
February 8	Analytical Method Validation	USP Headquarters, Rockville, MD
March 15	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
March 16	Standards 101: Advanced use of *USP–NF,* General Notices, & Monograph Chapters	USP Headquarters, Rockville, MD
March 22 and 23	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
April 11	Basic Statistics and their Practical Applications to the USP	USP Headquarters, Rockville, MD
May 18	Analytical Method Validation	USP Headquarters, Rockville, MD
July 18 and 19	Fundamentals of Dissolution	USP Headquarters, Rockville, MD

Calendar of Pharmacopeial Education Courses, 2005 *(Continued)*

Date	Name of course	Location
August 12	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
August 17	Analytical Method Validation	USP Headquarters, Rockville, MD
August 18	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
August 19	Standards 101: Advanced use of *USP–NF,* General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
October 19 and 20	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 7	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 8	Standards 101: Advanced use of *USP–NF,* General Notices, & Monograph Chapters	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.

Publication and Comment Schedule for *USP 28–NF 23*

Publication	**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. 2005*	Apr. 1, 2005*
PF 31(2) [Mar.–Apr. 2005]	Mar. 2005*	Not Applicable
2nd IRA [published in *PF* 31(2)]	Mar. 2005*	Apr. 1, 2005*
PF 31(3) [May–June 2005]	May 2005*	Not Applicable
3rd IRA [published in *PF* 31(3)]	May 2005*	June 1, 2005*
2nd Supplement	June 2005*	Aug. 1, 2005*
PF 31(4) [July–Aug. 2005]	July 2005*	Not Applicable
4th IRA [published in *PF* 31(4)]	July 2005*	Aug. 1, 2005*
PF 31(5) [Sept.–Oct. 2005]	Sept. 2005*	Not Applicable
5th IRA [published in *PF* 31(5)]	Sept. 2005*	Oct. 1, 2005*
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005*	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005*	Dec. 1, 2005*

* 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 (*USP27*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 27*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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.

FIRST INTERIM REVISION ANNOUNCEMENT to *USP 28* and to *NF 23*

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 February 1, 2005. **Released January 1, 2005.**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of *USF–NF* users.

USP Alcohol RS (May 1, 2005)
USP Alcohol Determination–Acetonitrile RS (March 1, 2005)
USP Alcohol Determination–Alcohol RS (March 1, 2005)
USP Amiodarone Hydrochloride RS (July 1, 2005)
USP Amlodipine Besylate RS (May 1, 2005)
USP Ammonium Carbonate (AS)
USP Ammonium Phosphate Dibasic (AS)
USP Benazepril Related Compound C RS (January 1, 2005)
USP Boric Acid (AS)
USP Butylated Hydroxytoluene RS (March 1, 2005)
USP Calcium Acetate (AS)
USP Calcium Carbonate (AS)
USP Calcium Chloride (AS)
USP Calcium Hydroxide (AS)
USP Calcium Stearate (AS)
USP Calcium Sulfate (AS)
USP Candelilla Wax RS (March 1, 2005)
USP Caprylocaproyl Polyoxylglycerides RS (March 1, 2005)
USP Cefpodoxime Proxetil RS (January 1, 2005)
USP Cellaburate (cellulose acetate butyrate) RS (May 1, 2005)
USP Powdered Black Cohosh Extract RS (March 1, 2005)
USP Corn Oil (AS)
USP Cottonseed Oil (AS)
USP Dehydrated Alcohol RS (May 1, 2005)
USP Dextran 1 RS (July 1, 2005)
USP Dextran T-10 RS (July 1, 2005)
USP Dibutyl Phthalate RS (March 1, 2005)
USP Dibutyl Sebacate (AS)
USP Fenbendazole Related Compound A RS (January 1, 2005)
USP Fenbendazole Related Compound B RS (January 1, 2005)
USP Ferrous Sulfate (AS)
USP Fexofenadine Hydrochloride RS (July 1, 2005)
USP Fexofenadine Related Compound A RS (July 1, 2005)
USP Fexofenadine Related Compound B RS (July 1, 2005)
USP Fluconazole RS (July 1, 2005)
USP Fluconazole Related Compound A RS (July 1, 2005)
USP Fluconazole Related Compound B RS (July 1, 2005)
USP Fluconazole Related Compound C RS (July 1, 2005)
USP Gemcitabine Hydrochloride RS (March 1, 2005)
USP Glacial Acetic Acid (AS)
USP Homopolymer Polypropylene RS (January 1, 2005)
USP Hypromellose Acetate Succinate RS (July 1, 2005)
USP Lactase RS (May 1, 2005)
USP Lactic Acid (AS)
USP Lauroyl Polyoxylglycerides (AS)
USP Leuprolide Acetate RS (January 1, 2005)
USP Linoleoyl Polyoxylglycerides RS (January 1, 2005)
USP Loratadine Related Compound A RS (May 1, 2005)
USP Loratadine Related Compound B RS (May 1, 2005)
USP Losartan Potassium RS (July 1, 2005)
USP Magnesium Carbonate (AS)
USP Magnesium Chloride (AS)
USP Magnesium Hydroxide (AS)
USP Magnesium Stearate (AS)
USP Magnesium Sulfate (AS)
USP Mangafodipir Related Compound A RS (July 1, 2005)
USP Mangafodipir Related Compound B RS (July 1, 2005)
USP Mangafodipir Trisodium RS (July 1, 2005)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Mirtazapine RS (March 1, 2005)
USP Nabumetone Related Compound A RS (May 1, 2005)
USP Nevirapine Anhydrous RS (March 1, 2005)
USP Nevirapine Hemihydrate RS (January 1, 2005)
USP Nevirapine Related Compound A RS (January 1, 2005)
USP Nevirapine Related Compound B RS (January 1, 2005)
USP Ondansetron Resolution Mixture RS (May 1, 2005)
USP Oxybutynin Related Compound B RS (January 1, 2005)
USP Oxybutynin Related Compound C RS (January 1, 2005)
USP Oleoyl Polyoxylglycerides RS (January 1, 2005)
USP Olive Oil (AS)
USP Palm Oil (AS)
USP Paroxetine Related Compound F RS (May 1, 2005)
USP Paroxetine Related Compound G RS (May 1, 2005)
USP Peanut Oil (AS)
USP Phenothiazine (AS)
USP Phenoxyethanol RS (July 1, 2005)
USP Phosphoric Acid (AS)
USP Polysorbate 20 (AS)
USP Polysorbate 40 (AS)
USP Polysorbate 60 (AS)
USP Polysorbate 80 (AS)
USP Potassium Benzoate (AS)
USP Potassium Bicarbonate RS (January 1, 2005)
USP Potassium Carbonate (AS)
USP Potassium Chloride (AS)
USP Potassium Iodide (AS)
USP Potassium Sorbate (AS)
USP Propionic Acid (AS)
USP Residual Solvent Class 2—Chlorobenzene RS (January 1, 2005)
USP Residual Solvent Class 2—Chloroform RS (May 1, 2005)
USP Residual Solvent Class 2—Cyclohexane RS (May 1, 2005)
USP Residual Solvent Class 2—1,2-Dichloroethene RS (March 1, 2005)
USP Residual Solvent Class 2—1,2-Dimethoxyethane RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS (May 1, 2005)
USP Residual Solvent Class 2—1,4-Dioxane RS (January 1, 2005)
USP Residual Solvent Class 2—2-Ethoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Formamide RS (May 1, 2005)
USP Residual Solvent Class 2—Methanol RS (January 1, 2005)
USP Residual Solvent Class 2—Methylbutylketone RS (May 1, 2005)
USP Residual Solvent Class 2—Methylcyclohexane RS (March 1, 2005)
USP Residual Solvent Class 2—Methylene Chloride RS (January 1, 2005)
USP Residual Solvent Class 2—*N*-Methylpyrrolidone RS (May 1, 2005)
USP Residual Solvent Class 2—2-Methoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Mixture A RS (May 1, 2005)
USP Residual Solvent Class 2—Mixture C RS (May 1, 2005)
USP Residual Solvent Class 2—Nitromethane RS (May 1, 2005)
USP Residual Solvent Class 2—Pyridine RS (May 1, 2005)
USP Residual Solvent Class 2—Sulfolane RS (May 1, 2005)
USP Residual Solvent Class 2—Tetrahydrofuran RS (January 1, 2005)
USP Residual Solvent Class 2—Tetralin RS (May 1, 2005)
USP Residual Solvent Class 2—Toluene RS (January 1, 2005)

USP Residual Solvent Class 2—Trichloroethylene RS (May 1, 2005)
USP Residual Solvent Class 2—Xylenes RS (January 1, 2005)
USP Sevoflurane Related Compound B RS (July 1, 2005)
USP Sevoflurane Related Compound C RS (July 1, 2005)
USP Sodium Acetate (AS)
USP Sodium Bicarbonate (AS)
USP Sodium Carbonate Anhydrous (AS)
USP Sodium Chloride (AS)
USP Sodium Citrate (AS)
USP Sodium Metabisulfite (AS)
USP Sodium Nitrite (AS)
USP Sodium Sulfate Anhydrous (AS)
USP Sodium Thiosulfate (AS)
USP Titanium Dioxide (AS)
USP Tolcapone RS (July 1, 2005)
USP Zinc Oxide (AS)
USP Zinc Sulfate (AS)

The official dates of any *USP 28* or *NF 23* 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 Bupropion Hydrochloride Related Compound A RS
USP Bupropion Hydrochloride Related Compound B RS
USP Bupropion Hydrochloride Related Compound C RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Bupropion Hydrochloride Related Compound F RS
USP Cinoxate 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 Maltose Monohydrate 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 Propofol RS
USP Propofol Related Compound A RS
USP Propofol Related Compound B RS
USP Propofol Resolution RS
USP Propofol for System Suitability RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Terbutaline Related Compound A 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

MONOGRAPHS (USP)

Bisoprolol Fumarate Tablets

Delete the following:

•**Water,** *Method I* ⟨921⟩: not more than 3.0%.•

Change to read:

Assay—

Diluent—Prepare a mixture of water and acetonitrile (65:35).

Mobile phase—•To a 1-L portion of *Diluent* add• 5 mL of heptafluorobutyric acid, 5 mL of diethylamine, and 2.5 mL of formic acid. Mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution in *Diluent* having a concentration of 0.5 mg of propranolol hydrochloride per mL and 1.0 mg of bisoprolol fumarate per mL.

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Bisoprolol Fumarate RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

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 bisoprolol fumarate, to a 25-mL volumetric flask. Add 10 mL of *Diluent,* and sonicate for 10 minutes. Cool, dilute with *Diluent* to volume, and mix. Centrifuge for 20 minutes, and use the clear supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 273-nm detector and a 4.6-mm × 12.5-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between bisoprolol and propranolol is not less than 7.0. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the tailing factor for the analyte peak 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 areas for the major peaks. Calculate the quantity, in mg, of bisoprolol fumarate [$(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$] 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 Bisoprolol Fumarate 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.

Glucagon

Change to read:

Assay—[NOTE—All buffers have a final pH of 7.4, unless otherwise indicated.]

HEPATOCYTE PREPARATION—

Calcium-free perfusion buffer with dextrose—Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 1.80 g of dextrose, 0.19 g of edetic acid, and 2.38 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid. Oxygenate prior to circulation.

Collagenase buffer—Prepare a solution containing, in each L, 3.62 g of sodium chloride, 23.83 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, 0.35 g of potassium chloride, 0.52 g of calcium chloride, and 1.8 g of dextrose. Adjust to a pH of 7.6, and oxygenate. Immediately before perfusion, dissolve a quantity of collagenase in this solution to obtain a concentration of 0.02% to 0.05%.

Wash buffer—Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 0.19 g of edetic acid, 2.38 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, 0.22 g of calcium chloride, and 0.12 g of magnesium sulfate.

Incubation buffer—Prepare a solution containing, in each L, 6.19 g of sodium chloride, 0.35 g of potassium chloride, 0.22 g of calcium chloride, 0.12 g of magnesium sulfate, 0.16 g of monobasic potassium phosphate, 11.915 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, and 1% bovine serum albumin. Adjust to a pH of 7.5.

Test animals—Male Sprague-Dawley rats are maintained on a standard rat chow diet and freely given water. On the morning of the test, select a healthy rat weighing approximately 300 g, and administer 100 Units of Heparin Sodium subcutaneously.

Procedure—[NOTE—Conduct this procedure in the morning to ensure that the rat has optimal glycogen in its liver.] Anesthetize the rat with an appropriate anesthetic. Open the abdominal cavity, and isolate the portal vein. Insert an angiocatheter connected to a perfusion pump, and tie into the portal vein at the general location of the lienal branch. Start the perfusion (25 mL per minute) in situ with *Calcium-free perfusion buffer with dextrose,* equilibrated with oxygen, at a temperature of 37°. As the liver enlarges, cut the inferior vena cava to allow pressure equilibrium. [NOTE—About 300 mL of the perfusate is needed to clear the liver of red blood cells at a flow rate of 30 to 60 mL per minute.] Then circulate *Collagenase buffer* at a flow rate of 30 to 60 mL per minute for about 10 minutes. The exact concentration of collagenase (within the range of 0.02% to 0.05%) is determined empirically for each lot of enzyme. The concentration of collagenase is that necessary to consistently cause a breakdown of the liver about 10 minutes after initial entry of the *Collagenase buffer* into the liver. When the liver significantly increases in size, changes color and consistency, and starts to leak perfusate out of the lobes, change the system to the oxygenated prewarmed *Wash buffer.* About 100 mL of *Wash buffer* is needed to wash the liver of collagenase at a flow rate of 25 mL per minute. Surgically remove the liver from the animal and place in a prewarmed tray containing oxygenated *Wash buffer* (37°). Gently comb the liver with a stainless steel, fine-toothed comb to free the hepatocytes. Wash the hepatocytes with *Wash buffer,* and filter through cheesecloth (or a 150-µm mesh polyethylene net) into a plastic beaker. Centrifuge the cell suspension for about 2 minutes at about 25 × *g* to form a loosely packed pellet. Discard the supernatant, and resuspend the pellet in *Wash buffer.* Repeat the washing procedure twice for a total of three washes. Resuspend the final pellet in 100 to 200 mL of *Incubation buffer,* depending on cell yield. [NOTE—If the *Assay* procedure is interrupted, cool the cells by collecting the cells in a beaker placed in ice. The cells are washed with ice-cold *Wash buffer,* and stored on ice until ready for use. At that point the cells are pelleted once more, and resuspended in ice-cold *Incubation buffer.*]

Suitability—The concentrations of cells may vary due to the collagenase activity and the viability of the hepatocytes. To check cell viability and to determine viable cell concentration, dilute duplicate 100-µL aliquots of cell suspension with 400 µL of *Wash buffer* and 500 µL of isotonic 0.4% trypan blue. The aliquots are counted in a hemocytometer. The cells are suspended in *Incubation buffer*

to obtain a viable cell concentration of not less than 3×10^6 per mL. Count several distinct fields. [NOTE—Viable cells are those cells that exclude the trypan blue.]

NEGATIVE CONTROL SOLUTION—Prepare a solution containing 0.5% bis(trimethylsilyl)acetamide (BSA) in sterile water.

INCUBATION FLASKS—Use 25-mL conical flasks, the bottoms of which have been heated and pushed inward to form a conically raised center.

STANDARD PREPARATIONS—In duplicate, dissolve a suitable quantity of USP Glucagon RS, accurately measured, in 0.01 N hydrochloric acid or other suitable diluent to obtain a solution containing 1.0 USP Glucagon Unit per mL. All dilutions thereafter are made using 0.5% BSA (w/v) in water. Accurately dilute measured volumes of each solution with *Negative control solution* to obtain five concentrations—200, 100, 50, 25, and 12.5 micro-Units per mL—of each solution *(Standard preparations).* Pipet 0.2 mL of each *Standard preparation* into separate *Incubation flasks.* Pipet 0.2 mL of *Negative control solution* into each of two flasks *(Negative control solutions 1* and *2).* Then add the hepatocytes into each of the 12 flasks.

ASSAY PREPARATIONS—Using accurately weighed quantities of Glucagon, proceed as directed for *Standard preparations.*

D-GLUCOSE DETERMINATION—

Standard stock solution—Transfer 2.0 g of USP Dextrose RS, accurately weighed, to a 200-mL volumetric flask; and dissolve in and dilute with saturated benzoic acid solution to volume.

Standard solutions—Transfer suitable quantities of *Standard stock solution* to three flasks, and dilute with saturated benzoic acid solution to obtain solutions having known concentrations of 0.5, 1.0, and 1.5 times the typical sample glucose concentration.

Potassium ferrocyanide solution—Dissolve 1.25 g of trihydrate potassium ferrocyanide in 125 mL of *Sterile Water for Injection.*

System suitability—Analyze the *Potassium ferrocyanide solution,* the *Standard solutions,* and five replicates of the middle *Standard solution.* Prepare a standard curve using the *Standard solutions* as directed for *Procedure:* the relative standard deviation of the standard curve is not more than 2.0%; the response of the *Potassium ferrocyanide solution* is not more than 30 mg per L; and the relative standard deviation is not more than 2.0% for the replicate analyses of the middle *Standard solution.*

PROCEDURE—Dispense 5 mL of *Hepatocyte preparation* into the special incubation flasks in sequence from high glucagon concentration to low glucagon concentration, alternating the *Standard preparations* with the *Assay preparations.* The flasks are swirled in an orbiting water bath at 125 rpm at 30° for approximately 30 to 60 minutes. NOTE—The exact incubation time must be determined to optimize the signal-to-noise ratio. Following incubation, place 0.5- to 1.0-mL aliquots, in duplicate, from each incubation flask into labeled tubes, and centrifuge at $12{,}500 \times g$. Determine the percentage of glucose concentration in each flask's supernatant.

To conform to the linear range of the instrument being used, it may be necessary to adjust by dilution each of the preparations. Use a glucose analyzer that has demonstrated appropriate specificity, accuracy, precision, and linear response over the range of concentrations being determined. [NOTE—A suitable analyzer may use an immobilized, oxidase-enzyme membrane or jacket-generating hydrogen peroxide, which is then detected at the electrode.] Perform the glucose analysis in the following sequence: *Negative control solution 1, Standard preparations, Assay preparations,* and *Negative control solution 2.* Determine the percentage of glucose against the *Negative control solution* for each preparation.

CALCULATIONS—

Linearity test—Use an analysis of variance (ANOVA) with one sample assayed against a standard, and using two replicates each, construct a table (see *Table 1*). Compare the value of the ratio $MSNL/MSRES_1$ to a critical value obtained from a table for an F distribution with $m-2$ and $3m-3$ degrees of freedom, where m is the number of dose levels for each preparation. If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity (ratio value is lower than the critical value), then proceed to the test for parallelism. If the ratio exceeds the critical value (significance level of 0.05), the nonlinearity is statistically significant and the test is repeated, discarding the results from either the highest or lowest dose of both the *Standard preparations* and the *Assay preparations* (four dose levels). If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity, then proceed to the test for parallelism.

Parallelism test—Compare the ratio $MSNP/MSRES_2$ to a critical value obtained from an F distribution having 1 and $4m-5$ degrees of freedom. If the ratio $MSNP/MSRES_2$ does not indicate the presence of significant nonparallelism, then the assay is considered valid. Use the appropriate dose levels for the estimation of the relative potency.

Relative potency—Calculate the relative potency, R, of the *Assay preparations* as compared with the *Standard preparations* as follows.

(1) X_j is defined as the $\log_{10}$ of the j^{th} dose of the *Standard preparations* or the *Assay preparations.* The glucagon dose varies from 12.5 to 200×10^{-6} USP Glucagon Units per mL. For ease in the subsequent calculations, these doses are respectively represented by 1 through 5, as shown in the table below.

j	1	2	3	4	5
Dose	12.5	25	50	100	200
X_j	1.10	1.40	1.70	2.00	2.30

(2) To differentiate between the *Standard preparations* and the *Assay preparations* in the calculations, the subscript i will be used, with $i = 1$ to designate the *Standard preparations* and $i = 2$ to designate the *Assay preparations.* Y_{ijk} will denote the glucose concentration associated with the k^{th} replicate of the j^{th} dose of the i^{th} preparation. For example, Y_{1jk} is the glucose concentration associated with the k^{th} replicate of the j^{th} dose of the appropriate *Standard preparation;* Y_{11k} is the glucose concentration associated with the k^{th} replicate of dose 1 of the *Standard preparation;* and Y_{21k} is the glucose concentration associated with the k^{th} replicate of dose 1 of the *Assay preparation.* Dose 1 represents a glucose dose of 12.5×10^{-6} USP Glucagon Units per mL. Finally, Y_{132} represents the glucose concentration associated with the 2nd replicate of dose 3 for the *Standard preparation.*

(3) Y_S and Y_t denote the average glucose concentrations for the *Standard preparations* and the *Assay preparations,* respectively.

(4) Calculate the least-squares slope estimate, b, for a linear regression relating the Y_{ijk}'s to the X_j's as follows: $b = S_{xy}/S_{xx}$, with S_{xy} and S_{xx} calculated using the equations in *Table 2.*

(5) The log potency, M, is calculated using $M = -1[(Y_S - Y_t)/b]$.

(6) R = antilog *(M).*

(7) Calculate the confidence limits (upper and lower) for the relative potency, R, using the value $s^2 = MSRES_3$ (see *Table 1* and *Table 2*) as follows. Obtain t from a table for a t distribution having $4m-4$ degrees of freedom. For the 95% limits, the t values can be obtained from *Table 9* under *Design and Analysis of Biological Assays* ⟨111⟩.

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NOTE—For confidence limits having other probability levels (i.e., 100(1 – *a*) %), the right tail *t* critical value having *a*/2 area to its right is used.

$$\text{Calculate } g = t^2S^2 / b^2S_{xx}$$

$$\text{and } F = (ts / b)\sqrt{(1/m)(1-g) + (M^2 / S_{xx})},$$

and calculate

$$M_L = (M - F)/(1 - g),$$

and

$$M_U = (M + F)/(1 - g),$$

where M is the log potency and M_L and M_U are the log potency lower and upper confidence limits. The lower and upper confidence limits for the relative potency, R, are given by

$$RL = \text{antilog } (M_L)$$

$$RU = \text{antilog } (M_U)$$

It meets the requirements if the potency is between 0.8 and 1.25 USP Glucagon Units per mg, and the confidence interval width at $P = 0.95$ does not exceed 45% of the computed potency. •Repeat the assay if the confidence interval width exceeds 45% of the computed potency.•1

Table 1. ANOVA for the Rat Hepatocyte Assay for Glucagon

Source	Degrees of Freedom	SS (Sum of Squares)	MS (Mean Square)
Preparations	1	SSPREP	MSPREP
Replicates	1	SSREP	MSREP
Linear Slope	1	SSLIN	MSLIN
Residual_3	$4m - 4$	SSRES_3	MSRES_3
Nonparallelism	1	SSNP	MSNP
Residual_2	$4m - 5$	SSRES_2	MSRES_2
Nonlinearity	$m - 2$	SSNL	MSNL
Residual_1	$3m - 3$	SSRES_1	MSRES_1
TOTAL	$4m - 1$	SST	

NOTES—This analysis pertains to one sample assayed against a standard, using two replicates each.

The number of dose levels for each preparation is denoted by *m*. *Table 2* gives the equations for calculating the SS terms.

In each row of the ANOVA table, the MS is obtained by dividing the SS term by the degrees of freedom.

Table 2. Equations for Calculating the Sums of Squares in the Analysis of Variance*

$$Y_{i..} = \sum_{jk}\sum y_{ijk}$$

$$Y_{.j.} = \sum_{ik}\sum y_{ijk}$$

$$Y_{..k} = \sum_{ij}\sum y_{ijk}$$

$$CF = \frac{\left(\sum_{ijk}\sum\sum y_{ijk}\right)^2}{4m}$$

$$S^S_{xy} = \sum_{jk}\sum x_j y_{1jk} - \frac{\left(\sum_j x_j\right)(Y_{1..})}{m}$$

$$S^T_{xy} = \sum_{jk}\sum x_j y_{2jk} - \frac{\left(\sum_j x_j\right)(Y_{2..})}{m}$$

$$S_{xy} = S^S_{xy} + S^T_{xy}$$

$$S^S_{xx} = 2\sum_j x_j^2 - \frac{2\left(\sum_j x_j\right)^2}{m}$$

$$S^T_{xx} = S^S_{xx}$$

$$S_{xx} = S^S_{xx} + S^T_{xx}$$

$$SSPREP = \frac{\sum_i Y^2_{i..}}{2m} - CF$$

$$SSREP = \frac{\sum_k Y^2_{..k}}{2m} - CF$$

$$SSLIN = \frac{\left(S_{xy}\right)^2}{S_{xx}}$$

$$SST = \sum_{i\,j\,k}\sum\sum y^2_{ijk} - CF$$

$$SSRES_3 = SST - SSPREP - SSREP - SSLIN$$

$$SSNP = \frac{\left(S^S_{xy}\right)^2}{S^S_{xx}} + \frac{\left(S^T_{xy}\right)^2}{S^T_{xx}} - SSLIN$$

$$SSRES_2 = SSRES_3 - SSNP$$

$$SSNL = \frac{\sum_j Y^2_{.j.}}{4} - SSLIN - CF$$

$$SSRES_1 = SSRES_2 - SSNL$$

* Refer to the *Calculations* for section on *Relative Potency* for the definitions of x_j and y_{ijk}.

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:

USP Betamethasone Sodium Phosphate RS—•Do not dry.•(1) Determine the water content titrimetrically at time of use. Keep container tightly closed. Store in a dry place. This material is hygroscopic.

Change to read:

USP Caffeine RS—•Do not dry. Keep container tightly closed. Protect from light.•(1)

Change to read:

USP Ceftriaxone Sodium RS—Do not dry before using. •For quantitative applications, determine the water content titrimetrically at the time of use. Store in a refrigerator. Keep container tightly closed.•(1)

Change to read:

USP Dexchlorpheniramine Maleate RS—•Do not dry.•(1) Keep container tightly closed. Protect from light. •Store in a refrigerator.•(1)

Change to read:

USP Dextran 1 RS—•Dry portion at 105° for 5 hours before use. Keep container tightly closed. Store in a desiccator.•(1)

Change to read:

▲**USP Fluconazole RS**—•Do not dry. Keep container tightly closed and avoid exposure to > 70% relative humidity. Protect from light.•(1)▲*USP28*

Change to read:

USP Fluconazole Related Compound B RS [2-(4-fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)-propan-2-ol]—•Do not dry. Keep container tightly closed. Protect from light.•(1)

Change to read:

USP Gentamicin Sulfate RS—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 110° for 3 hours before using. •Handle the dry material quickly and in a dry atmosphere.•(1) Keep container tightly closed. Protect from light. Store in a cold place.

Change to read:

USP Homosalate RS—•Do not dry. Keep container tightly closed.•(1)

Change to read:

USP Isradipine Related Compound A RS [isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate] ($C_{19}H_{19}N_3O_5$ ✧ 369.38)—•Do not dry.•(1) Keep container tightly closed, protected from light, and store in a freezer.

Change to read:

USP Lanolin Alcohols RS—Do not dry. •Keep container tightly closed. Protect from light.•(1)

Change to read:

USP Mangafodipir Trisodium RS [manganese(II) dipyridoxal diphosphate]—•Do not dry. Hygroscopic. For quantitative applications, determine the water content titrimetrically at the time of use. After opening vial, store tightly closed in a desiccator. Store in a refrigerator.•(1)

Change to read:

USP Mangafodipir Related Compound A RS [manganese(II) dipyridoxal monophosphate •sodium salt]—Do not dry. Hygroscopic. After opening vial, store tightly closed in a desiccator. Store in a refrigerator.•(1)

Change to read:

USP Mangafodipir Related Compound B RS [manganese(II) dipyridoxal diphosphate mono overalkylated •sodium salt]—Do not dry. Hygroscopic. After opening vial, store tightly closed in a desiccator. Store in a refrigerator.•(1)

Change to read:

USP Mangafodipir Related Compound C RS [manganese(II) dipyridoxal diphosphate •sodium salt]—Do not dry. Hygroscopic. After opening vial, store tightly closed in a desiccator. Store in a freezer.•(1)

Change to read:

USP Methacycline Hydrochloride RS—•Do not dry.•(1) Keep container tightly closed. Protect from light. •Store in a freezer.•(1)

Change to read:

USP Methohexital RS—•Do not dry.•(1) Keep container tightly closed.

Change to read:

USP Methyl Caprylate RS—Do not dry before using. After opening ampul, store in a tightly closed container, protected from light. •Store in a freezer.•(1)

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Change to read:

USP Nandrolone Decanoate RS—Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed. Protect from light. Store in a •freezer.•1

Change to read:

USP Paroxetine Related Compound B RS **[**trans-4-phenyl-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine •hydrochloride**]**—Do not dry. This is a hydrochloride salt.•1 Keep container tightly closed. Protect from light.

Change to read:

USP Parthenolide RS—Do not dry before using. Keep container tightly closed. Protect from light. Store in a freezer. ••1

Change to read:

▲**USP Phenoxyethanol RS** •**[**2-phenoxyethanol**]**—Do not dry. Keep container tightly closed. Protect from light.•1▲*USP28*

Change to read:

USP Prednisolone RS—•This is the anhydrous form.•1 Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed. •Protect from light.•1

Change to read:

USP Prednisone RS—•Do not dry.•1 Keep container tightly closed.

Change to read:

USP Quinic Acid RS—Do not dry before using. Keep container tightly closed and protected from light. ••1 Store in a freezer.

Change to read:

USP Silybin RS—Do not dry before using. ••1 Keep container tightly closed and protected from light. Store in a freezer.

Change to read:

USP Terbutaline ••1 Related Compound A RS **[**3,5-dihydroxy-ω-*t*-butylaminoacetophenone sulfate**]**—Do not dry. •Keep container tightly closed.•1

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ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
464	*Cholecalciferol Solution*	*Assay*	Line 18 under *Precholecalciferol response factor*: Change the formula "$C'_{pre}r_p$," to: C'_{pre}/r_p,
1217	*Meropenem*	*Chromatographic purity*	Line 18 under *Procedure*: Change "Not more than 0.3% of any two major impurities is found, calculated on the dried basis; not more than 0.1% of any other impurity is found, calculated on the dried basis;" to: Not more than 0.3% of any two major impurities is found, calculated on the anhydrous basis; not more than 0.1% of any other impurity is found, calculated on the anhydrous basis;

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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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24*; and

■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*, ■2S (*USP 28*) indicates that the proposed revision is slated for the *Second Supplement to USP 28*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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.

MONOGRAPHS (USP)

BRIEFING

Albuterol Tablets, *USP 28* page 58 and page 50 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to revise the *Procedure* in the *Assay* by correcting the formula so that it reflects the final volume of the *Assay preparation*.

(PA1: K. Russo) RTS—41888-1

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

▲ ▲*USP29*
⟨711⟩—

Medium: water; 500 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.

Determine the amount of $C_{13}H_{21}NO_3$ dissolved using the following method.

Mobile phase, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Procedure—

▲Proceed as directed for *Procedure for Capsules, Uncoated Tablets,* and *Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.▲*USP29*
Inject a suitable volume (about 100 µL) of ~~a portion of the solution under test,~~

▲the pooled sample,▲*USP29*
previously filtered through a 0.45-µm nylon filter, into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{13}H_{21}NO_3$ dissolved by comparing this peak response with the major peak response similarly obtained on chromatographing the *Standard preparation* previously diluted, if necessary, with a mixture of water and methanol (6 : 4) to obtain a Standard solution having a known concentration of USP Albuterol Sulfate RS approximately corresponding to the concentration of the solution under test.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{13}H_{21}NO_3$ is dissolved in 30 minutes:

▲the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q,* is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

▲*USP29*

Change to read:

Assay—

1% Acetic acid—Transfer a 20-mL portion of glacial acetic acid to a suitable volumetric flask, and dilute with water to 2000 mL.

Mobile phase—Dissolve 1.13 g of sodium 1-hexanesulfonate in 1200 mL of water, add 12 mL of glacial acetic acid, and mix. Prepare a filtered and degassed mixture of this solution and methanol (6 : 4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12 mg of USP Albuterol Sulfate RS, accurately weighed, to a 100-mL volumetric flask. Add 60 mL of *1% Acetic acid,* sonicate for 5 minutes, dilute with methanol to volume, and mix. Pipet 25 mL of this solution into a 100-mL volumetric flask, dilute with a mixture of water and methanol (6 : 4) to volume, and mix.

Assay preparation—Transfer a number of whole Tablets, equivalent to about 50 mg of albuterol, to a 2000-mL volumetric flask. Add 1200 mL of *1% Acetic acid*, shake by mechanical means for 45 minutes, sonicate for 10 minutes, allow to cool to room temperature, dilute with methanol to volume, and mix. Pass through a suitable filter having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 276-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 preparation,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 800 theoretical plates; the tailing factor for the analyte peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

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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 albuterol ($C_{13}H_{21}NO_3$) in the number of Tablets taken by the formula:

~~$2(239.32/576.71)200C(r_u/r_s),$~~

~~in which 239.32 and 576.71 are the molecular weights of albuterol and albuterol sulfate, respectively; *C* is the concentration, in mg per mL, of USP Albuterol Sulfate 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.~~

▲$2000(239.31/576.70)C(r_U/r_S),$

in which 2000 is the volume, in mL, of the *Assay preparation;* 239.31 and 576.70 are the molecular weights of albuterol and albuterol sulfate, respectively; *C* is the concentration, in mg per mL, of USP Albuterol Sulfate 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.▲*USP29*

BRIEFING

Butabarbital Sodium Tablets, *USP 28* page 302. It is proposed to revise the test for *Uniformity of dosage units* to correct an invalid cross-reference to the *Butabarbital Sodium Capsules* monograph, which has been omitted from *USP.* It is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of June 1, 2005.

(PA3: R. Ravichandran) RTS—41943-1

Change to read:

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

~~*Acid–methanol mixture* and *Standard preparation*—Prepare as directed in the test for *Content uniformity* under *Butabarbital Sodium Capsules.*~~

•*Acid–methanol mixture*—Prepare a mixture of methanol and 1 N hydrochloric acid (9 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Butabarbital RS in *Acid–methanol mixture* to obtain a solution having a known concentration of about 0.45 mg per mL.•3

Test preparation—Transfer 1 finely powdered Tablet to a 25-mL volumetric flask, ~~and proceed as directed for *Test preparation* in the test for *Content uniformity* under *Butabarbital Sodium Capsules,* beginning with "add *Acid–methanol mixture* to volume."~~

•add *Acid–methanol mixture* to volume, and mix. Filter, discarding the first 5 mL of the filtrate, and dilute the subsequent filtrate quantitatively and stepwise if necessary, with *Acid–methanol mixture* to obtain a solution containing 0.5 to 0.6 mg of butabarbital sodium per mL.•3

Procedure—~~Proceed as directed for *Procedure* in the test for *Content uniformity* under *Butabarbital Sodium Capsules.*~~

•Transfer 2.0 mL each of the *Standard preparation* and the *Test preparation* to separate 100-mL volumetric flasks, and transfer 2.0 mL of *Acid–methanol mixture* to a third volumetric flask to provide a blank. Dilute each flask with pH 9.6 alkaline borate buffer (see under *Solutions* in the section *Reagents, Indicators, and Solutions*), and mix. Concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 240 nm, with a suitable spectrophotometer, using the blank to set the instrument.•3

Calculate the quantity, in mg, of $C_{10}H_{15}N_2NaO_3$ in the Tablet

•taken•3

by the formula: ~~given therein,~~

•$(234.23/212.25)/(TC/D)(A_U/A_S),$•3

in which 234.23 and 212.25 are the molecular weights of butabarbital sodium and butabarbital, respectively; *T* is the labeled quantity, in mg, of butabarbital sodium in the Tablet; *C* is the concentration, in ~~µg~~

•mg•3

per mL, of USP Butabarbital RS in the *Standard preparation; D* is the concentration, in ~~µg~~

•mg•3

per mL, of butabarbital sodium in the *Test preparation,* based upon the labeled quantity per Tablet and the extent of dilution; and A_U and A_S are the absorbances of the solutions from the *Test preparation* and the *Standard preparation,* respectively.

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BRIEFING

Cefaclor Extended-Release Tablets, *USP 28* page 371—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-48

Delete the following:

▲~~**Labeling**—The labeling indicates the *Drug Release Test* with which the product complies.~~▲*USP29*

BRIEFING

Ciprofloxacin Injection, *USP 28* page 478 and page 1596 of *PF* 30(5) [Nov.–Dec. 2004]. It is proposed to revise the Definition to use Water for Injection rather than Sterile Water for Injection.

(PA7b: B. Davani) RTS—41929-1

Change to read:

» Ciprofloxacin Injection is a sterile solution of Ciprofloxacin ▲or Ciprofloxacin Hydrochloride▲*USP28* in ~~Sterile Water for Injection~~

▲Water for Injection,▲*USP29*
in 5 percent Dextrose Injection, or in 0.9 percent Sodium Chloride Injection prepared with the aid of Lactic Acid. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

Change to read:

Limit of ciprofloxacin ethylenediamine analog—Proceed as directed in the *Assay* under *Ciprofloxacin*. Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the *Assay preparation* by the formula:

$$100[0.7r_A/(0.7r_A + r_C)],$$

in which 0.7 is the ~~response~~

■correction■1S *(USP28)*
factor for ciprofloxacin ethylenediamine analog; ~~relative to that of ciprofloxacin~~

■■1S *(USP28)*

and r_A and r_C are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than 0.5% of ciprofloxacin ethylenediamine analog.

Change to read:

Dextrose content *(if present)*—Using the undiluted Injection, determine the angular rotation in a suitable polarimeter tube ~~at 25° (see *Optical Rotation* ⟨781⟩). The observed rotation, in degrees, multiplied by 1.0425*A*, in which *A* is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in g, of $C_6H_{12}O_6 \cdot H_2O$ in each 100 mL of Injection taken: between 4.75 and 5.25 g of $C_6H_{12}O_6 \cdot H_2O$ is found.~~

■(see *Optical Rotation* ⟨781⟩). Calculate the percentage (g per 100 mL) of $C_6H_{12}O_6 \cdot H_2O$ in the portion of Injection taken by the formula:

$$(100/52.9)(198.17/180.16)AR,$$

in which 100 is the percentage; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; *A* is 100 mm divided by the length of the polarimeter tube, in mm; and *R* is the observed rotation, in degrees: between 4.75 and 5.25 g of $C_6H_{12}O_6 \cdot H_2O$ is found.■2S *(USP28)*

BRIEFING

Dyclonine Hydrochloride, *USP 28* page 706. It is proposed to revise the tests for *Identification* by replacing the UV absorption spectra comparison (test *B*) with an HPLC retention time agreement of the major peak in the chromatograms of the *Assay preparation* and the *Standard preparation,* in accordance with current policies.

(PA1: K. Russo) RTS—41743-5

Change to read:

Identification—
A: *Infrared Absorption* ⟨197M⟩.
B: ~~*Ultraviolet Absorption* ⟨197U⟩—~~
~~*Solution:* 25 µg per mL.~~

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▲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.*▲*USP29*

C: Add 2 mL of silver nitrate TS to 10 mL of Dyclonine Hydrochloride solution (1 in 100): a white precipitate is formed. Add 2 mL of nitric acid, centrifuge, and discard the supernatant. Wash the precipitate twice by adding 10 mL of 2 N nitric acid, centrifuging, and discarding the supernatant: the precipitate so obtained is soluble in 6 N ammonium hydroxide.

BRIEFING

Epinephrine Injection, *USP 28* page 740. It is proposed to revise the test for *Identification* with the addition of an HPLC retention time agreement of the major peak in the chromatograms of the *Assay preparation* and the *Standard preparation,* in accordance with current policies.

(PA1: K. Russo) RTS—41743-6

Change to read:

Identification~~— It responds to the *Identification* test under *Epinephrine Nasal Solution.*~~

▲**A:** It responds to the *Identification* test under *Epinephrine Nasal Solution*.

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.*▲*USP29*

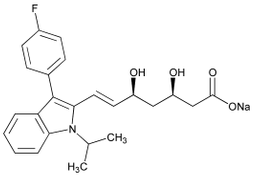
BRIEFING

Fluvastatin Sodium, page 1234 of *PF* 30(4) [July–Aug. 2004]; **Fluvastatin Capsules,** page 1237 of *PF* 30(4) [July–Aug. 2004]. It is proposed to change the composition of *USP Fluvastatin for System Suitability RS.* It will now contain fluvastatin sodium and three related impurities, including the ones previously proposed as *USP Fluvastatin Related Compound A RS* and *USP Fluvastatin Related Compound B RS*. This revision necessitates changes in the preparation of the *System suitability solution* in the test for *Chromatographic purity.* In addition, chemical names for related impurities are now included in *Table 1.* Finally, minor editorial style changes have been made.

(PA4: E. Gonikberg) RTS—42030-1

Add the following:

■Fluvastatin Sodium



$C_{24}H_{25}FNNaO_4$ 433.46

6-Heptenoic acid, 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-, monosodium salt, [*R**,*S**-(*E*)]-(±)-.

Sodium (±)-(3*R**,5*S**,6*E*)-7-[3-(*p*-fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoate [*93957-55-2*].

» Fluvastatin Sodium contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{25}FNNaO_4$, calculated on the anhydrous basis.

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Packaging and storage—Preserve in tight, light-resistant containers, protected from moisture. Store between 15° and 30°.

Change to read:

USP Reference standards ⟨11⟩—*USP Fluvastatin Sodium RS.* ~~*USP Fluvastatin Sodium Anti-Isomer RS. USP Fluvastatin Related Compound A RS. USP Fluvastatin Related Compound B RS.*~~ ▲▲*USP29* *USP Fluvastatin for System Suitability RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩.

C: A solution (0.2 in 1) meets the requirements of the flame test for *Sodium* ⟨191⟩.

pH ⟨791⟩**:** between 8.0 and 10.0, in a solution (1 in 100), the test being performed immediately after preparation.

Water, *Method I* ⟨921⟩**:** not more than 4.0%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Change to read:

Chromatographic purity—[NOTE—Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

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

~~*System suitability stock solution*—Prepare a solution in a mixture of methanol and acetonitrile (3 : 2) containing about 0.1 mg of USP Fluvastatin Related Compound A RS and about 0.1 mg of USP Fluvastatin Related Compound B RS per mL.~~ ▲▲*USP29*

System suitability solution—~~Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in 35 mL of *Solution B.* Add 5.0 mL of *System suitability stock solution* in-~~ ~~to the flask, dilute with *Solution A* to volume, and mix. [NOTE—The *System suitability stock solution and the System suitability solution* are stable for up to 6 months if stored in a refrigerator.~~ ▲Use the *System suitability preparation,* prepared as directed in the *Assay.* [NOTE—USP Fluvastatin for System Suitability RS contains Fluvastatin Sodium and three related impurities: fluvastatin anti-isomer, fluvastatin hydroxydiene, and fluvastatin *t*-butyl ester. The *System suitability solution* is stable for up to 6 months if stored in a refrigerator.]▲*USP29*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Chromatographic system—Proceed as directed in the *Assay,* except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure.* Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, fluvastatin hydroxydiene, and fluvastatin *t*-butyl ester. The resolution, *R,* between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.6; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the *Standard solution,* and record the peak responses at 305 nm 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 at 305 nm and 365 nm, identify the impurities listed in *Table 1,* and measure the peak responses. [NOTE—3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of 365 nm, and all

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other compounds are monitored at 305 nm.] Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin, in the portion of Fluvastatin Sodium taken by the formula:

$$100F(C_S / C_T)(r_{i\,(305)} / r_{S\,(305)}),$$

in which F is the relative response factor as listed in *Table 1* [NOTE—Use F equal to 1.0 for unknown impurities]; C_S is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Fluvastatin Sodium in the *Test solution;* $r_{i(305)}$ is the peak response at 305 nm for each impurity obtained from the *Test solution;* and $r_{S(305)}$ is the peak response at 305 nm for the fluvastatin peak, obtained from the *Standard solution.*

Calculate the percentage of 3-hydroxy-5-keto fluvastatin in the portion of Fluvastatin Sodium taken by the formula:

$$100F(C_S / C_T)(r_{i(365)} / r_{S\,(365)}),$$

in which F, C_S, and C_T are as defined above; $r_{i\,(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin, obtained from the *Test solution;* and $r_{S(365)}$ is the peak response at 365 nm for the fluvastatin peak, obtained from the *Standard solution.* 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 1.0% of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
Fluvastatin *N*-ethyl analog▲[2]▲*USP29*	0.7	0.9	0.1
Fluvastatin anti-isomer▲[3]▲*USP29*	1.2	1.0	0.8
3-Hydroxy-5-keto fluvastatin▲[4]▲*USP29*	1.5	0.037[1]	0.1
3-Keto-5-hydroxy fluvastatin▲[5]▲*USP29*	1.6	1.6	0.1
Fluvastatin hydroxy-diene~~[2]~~▲[6]▲*USP29*	2.0	1.1	0.1
Fluvastatin short chain aldehyde▲[7]▲*USP29*	3.0	0.7	0.1
Fluvastatin *t*-butyl ester ~~[3]~~▲[8]▲*USP29*	3.4	1.1	0.2

[1] At 365 nm

[2] ~~Fluvastatin related compound A~~▲[R*,S*-E]-(±)-7-[3-(4-Fluorophenyl)-1-ethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP29*

[3] ~~Fluvastatin related compound B~~▲[R*,R*-E]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP29*

▲[4] E-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3-hydroxy-5-oxo-6-heptenoic acid monosodium salt

[5] E-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3-oxo-5-hydroxy-6-heptenoic acid monosodium salt

[6] [E,E]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3-hydroxy-4,6-heptadienoic acid monosodium salt

[7] 3-(4-Fluorophenyl)-1-(methylethyl)-1H-indole]-2-carboxaldehyde

[8] [R*,S*-E]-(±)-7-[3-(4-fluorophenyl)-1-methylethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1,dimethylethyl ester▲*USP29*

Assay—

Solution A—Add 20 mL of 25% aqueous tetramethylammonium hydroxide solution to 880 mL of water. Adjust with about 2.3 mL of phosphoric acid to a pH of 7.2 ± 0.2. Add 100 mL of a mixture of methanol and acetonitrile (3 : 2), mix, and filter.

Solution B—Add 20 mL of 25% aqueous tetramethylammonium hydroxide solution and 80 mL of water to 900 mL of a mixture of methanol and acetonitrile (3 : 2). Adjust with about 2.3 mL of phosphoric acid to a pH of 7.2 ± 0.2, mix, and filter. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.*

System suitability preparation—Transfer an accurately weighed quantity of USP Fluvastatin for System Suitability RS to a suitable volumetric flask, dissolve first in *Solution B,* using 40% of the final volume, then dilute with *Solution A* to volume, and mix to obtain a solution having a known concentration of about 0.5 mg of fluvastatin sodium per mL.

Standard preparation—Transfer an accurately weighed quantity of USP Fluvastatin Sodium RS to a suitable volumetric flask, dissolve first in *Solution B,* using 40% of the final volume, then dilute with *Solution A* to volume, and mix to obtain a solution having a known concentration of about 0.5 mg of fluvastatin sodium per mL.

Assay preparation—Transfer about 25 mg of Fluvastatin Sodium, accurately weighed, to a 50-mL volumetric flask. Dissolve in 20 mL of *Solution B,* dilute with *Solution A* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 305-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing L1. The flow rate is about 3.0 mL per minute, and the column temperature is maintained at 35°. The chromatograph is programmed as follows. [NOTE—Adjust the start time of the gradient step and the equilibration time for each instrument.]

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6	60	40	isocratic
6–20	60→18	40→82	linear gradient
20–20.1	18→60	82→40	linear gradient
20.1–25.1	60	40	equilibration

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for fluvastatin and 1.2 for fluvastatin anti-isomer; the resolution, *R,* between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.6; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 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 fluvastatin peaks. Calculate the quantity, in mg, of $C_{24}H_{25}FNNaO_4$ in the portion of Fluvastatin Sodium taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the *Standard preparation;* and r_U and r_S are the fluvastatin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP28*)

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BRIEFING

Fluvastatin Capsules, page 1237 of *PF* 30(4)—See briefing under *Fluvastatin Sodium*.

(PA4: E. Gonikberg) RTS—42030-2

Add the following:

■Fluvastatin Capsules

» Fluvastatin Capsules contain an amount of Fluvastatin Sodium equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluvastatin ~~($C_{24}H_{25}FNO_4$)~~ $C_{24}H_{26}FNO_4$.

Packaging and storage—Preserve in tight, light-resistant containers, protected from moisture and light. Store in a cool place or at controlled room temperature.

Change to read:

USP Reference standards ⟨11⟩*—USP Fluvastatin Sodium RS.* ~~*USP Fluvastatin Sodium Anti-Isomer RS. USP Fluvastatin-Related Compound A RS.*~~ ▲*USP29* *USP Fluvastatin for System Suitability 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: A solution (0.2 in 1) meets the requirements of the flame test for *Sodium* ⟨191⟩.

Dissolution ⟨711⟩**—**

Medium: water; 500 mL.

Apparatus 2: 50 rpm, sinkers not used.

Time: 30 minutes.

Determine the amount of ~~$C_{24}H_{25}FNO_4$~~ $C_{24}H_{26}FNO_4$ dissolved by employing the following method.

Buffer solution—Dissolve about 1.534 g of monobasic ammonium phosphate in about 800 mL of water, and adjust with phosphoric acid or ammonium hydroxide to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (7 : 3).

Standard solution—[NOTE—A volume of methanol, not exceeding 2% of the final volume of solution, may be used to aid in dissolving the USP Reference Standard.] Dissolve an accurately weighed quantity of USP Fluvastatin Sodium RS in *Medium* to obtain a solution having a known concentration of fluvastatin corresponding to that obtained when 1 Capsule is dissolved in 500 mL of solvent.

Test solution—Withdraw 20-mL portions of liquid under test from each vessel, and pass through a suitable filter, discarding the first 2 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector, a suitable 7-µm guard column that contains packing L1, and a 4.6-mm × 10-cm column that contains 5-µm packing L1. The flow rate is about 2.0 mL per minute. 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%~~ 1.5%.

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 fluvastatin peaks. From the measured peak areas, calculate the quantity of ~~$C_{24}H_{25}FNO_4$~~ $C_{24}H_{26}FNO_4$ dissolved.

Tolerances—Not less than 80% *(Q)* of the labeled amount of ~~$C_{24}H_{25}FNO_4$~~ $C_{24}H_{26}FNO_4$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements, the *Chromatographic system* being prepared as directed for the *Dissolution* test.

Change to read:

Chromatographic purity—[NOTE—Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

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

~~*System suitability stock solution*—Prepare a solution in methanol containing about 0.1 mg of USP Fluvastatin Related Compound A RS per mL.~~ ▲▲*USP29*

System suitability solution—~~Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in 35 mL of methanol. Add 5.0 mL of *System suitability stock solution* into the flask, dilute with *Diluent* to volume, and mix. [NOTE—The *System suitability stock solution* and the *System suitability solution* are stable for up to 6 months if stored in a refrigerator.]~~ ▲Transfer an accurately weighed quantity of USP Fluvastatin for System Suitability RS to a suitable volumetric flask, dissolve first in *Solution B,* using 40% of the final volume, then dilute with *Solution A* to volume, and mix to obtain a solution having a known concentration of about 0.5 mg of fluvastatin sodium per mL. [NOTE—USP Fluvastatin for System Suitability RS contains fluvastatin sodium and three related impurities: fluvastatin anti-isomer, fluvastatin hydroxydiene, and fluvastatin *t*-butyl ester. The *System suitability stock solution* and the *System suitability solution* are stable for up to 6 months if stored in a refrigerator.]▲*USP29*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Chromatographic system—Proceed as directed in the *Assay,* except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure.* Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, and fluvastatin hydroxydiene. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure:* the resolution, *R,* between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.4; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms at 305 nm and 365 nm, identify the impurities listed in *Table 1,* and measure the peak responses. [NOTE—3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of 365 nm, and all other compounds are monitored at 305 nm.] Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin, in the portion of Capsules taken by the formula:

$$100F(411.48/433.46)(C_S / C_T)(r_{i(305)} / r_{S(305)}),$$

in which F is the relative response factor as listed in *Table 1* [NOTE—Use F equal to 1.0 for unknown impurities.]; 411.48 and 433.46 are the molecular weights of fluvastatin and fluvastatin sodium, respectively; C_S is the concentration, in mg

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per mL, of USP Fluvastatin Sodium RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fluvastatin in the *Test solution,* based on the label claim; $r_{i\,(305)}$ is the peak response at 305 nm for each impurity obtained from the *Test solution;* and $r_{S\,(305)}$ is the peak response at 305 nm for the fluvastatin peak, obtained from the *Standard solution*.

Calculate the percentage of 3-hydroxy-5-keto fluvastatin in the portion of Capsules taken by the formula:

$$100F(411.48/433.46)(C_S/C_T)(r_{i\,(365)}/r_{S(365)}),$$

in which F, C_S, and C_T are as defined above; $r_{i\,(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin, obtained from the *Test solution;* and $r_{S\,(365)}$ is the peak response at 365 nm for the fluvastatin peak, obtained from the *Standard solution.* In addition to not exceeding the limits for each impurity in *Table 1,* not more than 0.5% of any unknown impurity is found; not more than 1.5% of total unknown impurities is found; and not more than 4.0% of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Fluvastatin anti-isomer	1.2	1.0	1.5
3-Hydroxy-5-keto fluvastatin	1.6	0.037[1]	1.0
Fluvastatin hydroxy-diene[2] ▲*USP29*	2.2	1.1	1.0
Fluvastatin short-chain aldehyde	3.2	0.7	0.5

[1] At 365 nm
[2] ~~Fluvastatin related compound A~~ ▲*USP29*

Assay—

pH 7.2 Buffer—Prepare a solution containing 40 mL of 25% aqueous tetramethylammonium hydroxide in 1 L of water, and adjust with approximately 4.5 mL of phosphoric acid to a pH of 7.2 ± 0.2.

Methanol–acetonitrile mixture—Prepare a mixture of methanol and acetonitrile (3 : 2).

Solution A—Prepare a filtered and degassed mixture of *pH 7.2 Buffer* and *Methanol–acetonitrile mixture* (87.5 : 12.5).

Solution B—Prepare a filtered and degassed mixture of *Methanol–acetonitrile mixture* and *pH 7.2 Buffer* (87.5 : 12.5).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.*

Diluent—Prepare a mixture of *pH 7.2 Buffer* and *Methanol–acetonitrile mixture* (54 : 46).

System suitability preparation—Dissolve an accurately weighed quantity of USP Fluvastatin for System Suitability RS in *Diluent* to obtain a solution having a known concentration of about 0.42 mg of fluvastatin sodium per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Fluvastatin Sodium RS in *Diluent* to obtain a solution having a known concentration of about 0.42 mg of fluvastatin sodium per mL.

Assay stock preparation—Transfer the contents and the empty shells of 10 Capsules to a 200-mL glass-stoppered flask. Add 100.0 mL of methanol, and stir with a magnetic or a mechanical stirrer for 45 minutes. Centrifuge a portion of this solution at 4000 rpm for 20 minutes.

Assay preparation—Quantitatively transfer an amount of the *Assay stock preparation,* containing 20.0 mg of fluvastatin based on the label claim, to a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 305-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing Ll. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows. [NOTE—Adjust the start time of the gradient step and the equilibration time for each instrument.]

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6	54	46	isocratic
6–17	54→17	46→83	linear gradient
17–20	17	83	isocratic
20–20.1	17→54	83→46	linear gradient
20.1–26.1	54	46	equilibration

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the retention time of the fluvastatin peak is about 5.4 minutes; the relative retention times are about 1.0 for fluvastatin and 1.2 for fluvastatin anti-isomer; the resolution, *R,* between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.4; and the relative standard deviation for replicate injections is not more than 1.5%. [NOTE–If the retention time of the fluvastatin peak exceeds 5.7 minutes, adjust the isocratic step accordingly so that both the fluvastatin peak and the anti-isomer peak elute within the isocratic region.]

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 areas for the fluvastatin peaks. Calculate the quantity, in mg, of fluvastatin ($C_{24}H_{26}FNO_4$) in the portion of Capsules taken by the formula:

$$5000(411.48/433.46)(C/V)(r_U/r_S),$$

in which 411.48 and 433.46 are the molecular weights of fluvastatin and fluvastatin sodium, respectively; C is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the *Standard preparation;* V is the volume, in mL, of the *Assay stock preparation* taken to prepare the *Assay preparation;* and r_U and r_S are the fluvastatin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP28*)

BRIEFING

Gabapentin. The proposed new monograph for Gabapentin previously published on page 72 of *PF* 29(1) [Jan.–Feb, 2003] is hereby canceled and replaced with the following new proposal. It is proposed to revise the methods in the test for *Related compounds* and in the *Assay* to include impurities and acceptance criteria for approved products. The validation of the analytical procedures in *Method 1* of *Test 1* in the test for *Related compounds* and in the *Assay* was performed using a Luna C18 brand of L1 packing. The retention time for gabapentin is about 6 minutes. In *Method 2* of *Test 1* in the test for *Related compounds* the validation of the analytical procedures was performed using a Luna C18 brand of L1 packing. The retention time for gabapentin related compound D is about 17 minutes. *Test 2* in *Related compounds* was previously published on page 3004 of *PF* 27(5) [Sept.–Oct. 2001]; tests for this method used a Symmetry C8 brand of L7 column. The retention time for gabapentin is about 7.5 minutes.

(PA3: S. Salado) RTS—39923-1; 41257-1; 41450-1

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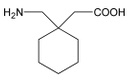
Add the following:

▲Gabapentin



$C_9H_{17}NO_2$ 171.24

Cyclohexaneacetic acid, 1-(aminomethyl)-.

1-(Aminomethyl)cyclohexaneacetic acid [*60142-96-3*].

» Gabapentin contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_{17}NO_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

Labeling—Label it to indicate with which impurity tests the article complies.

USP Reference standards ⟨11⟩**—***USP Gabapentin RS. USP Gabapentin Related Compound A RS. USP Gabapentin Related Compound B RS. USP Gabapentin Related Compound D RS. USP Gabapentin Related Compound E 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 6.5 and 8.0, in a solution (1 in 50).

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%.

Limit of chloride—Transfer about 1500 mg of Gabapentin, accurately weighed, to a 100-mL beaker, and dissolve in 50 mL of a mixture of water, methanol, and acetic acid (60 : 39 : 1). Titrate with 0.01 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections (see *Titrimetry* ⟨541⟩). Each mL of 0.01 N silver nitrate is equivalent to 0.3545 mg of chloride: not more than 0.01% is found.

Related compounds—[NOTE—Perform all related impurity tests unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to the manufacturer's material.]

TEST 1, METHOD 1—

Diluent, Buffer solution, Mobile phase, Impurities solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Standard solution—Use the *Standard 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 peak responses. Calculate the percentage of any impurity in the portion of Gabapentin taken by the formula:

$$2500F(C/W)\ (r_i / r_S),$$

in which F is the relative response factor of the impurity according the table below; C is the concentration, in mg per mL, of USP Gabapentin Related Compound E RS in the *Standard solution; W* is the weight, in mg, of Gabapentin, on an 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 gabapentin related compound E in the *Standard solution*: the impurities meet the requirements given in the table below.

Compound Name	Relative Response Factor	Limit (%)
Gabapentin related compound A	1.0	0.10
Gabapentin related compound B	1.0	0.06
Gabapentin related compound E	1.0	0.10
Individual unknown impurity	0.025	0.10

TEST 1, METHOD 2—

Diluent—Dissolve 2.32 g of ammonium phosphate monobasic in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Proceed as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* methanol, and acetonitrile (35 : 30 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Gabapentin Related Compound D RS in methanol, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.0028 mg per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 13,600 theoretical plates for the gabapentin related compound D peak; and the relative standard deviation for replicate injections is not more than 7.0%.

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 any impurity in the portion of Gabapentin taken by the formula:

$$2500(C/W)\,(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Gabapentin Related Compound D RS in the *Standard solution; W* is the weight, in mg, of Gabapentin, 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 gabapentin related compound D in the *Standard solution:* not more than 0.02% of gabapentin related compound D is found; not more than 0.10% of any other impurity is found; and not more than 0.35% of total impurities is found (including the impurities quantified in *Test 1* and *Test 2*). [NOTE—Disregard all the peaks having relative retention times of 0.35 or less.]

TEST 2—

Diluent—Dissolve 1.2 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5 N potassium hydroxide to a pH of 6.9.

Blank solution—Use the *Diluent*.

Solution A—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water, and adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, mix, filter, and degas.

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Solution B—Dissolve 1.2 g of monobasic potassium phosphate in 700 mL of water, adjust with 5 N potassium hydroxide to a pH of 6.9, add 300 mL of acetonitrile, mix, 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⟩).

Standard solution—Dissolve accurately weighed quantities of USP Gabapentin RS and USP Gabapentin Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.

Test solution—Transfer about 500 mg of Gabapentin, 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 5-µm packing L7. The flow rate is about 1.3 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–7	100	0	isocratic
7–45	100→0	0→100	linear gradient
45–45.1	0→100	100→0	linear gradient
45.1–48	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 4.8 for gabapentin related compound A and 1.0 for gabapentin; and the relative standard deviation for replicate injections in both peaks is not more than 10.0%.

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 responses for all the peaks. [NOTE—Disregard any peaks obtained from the *Blank solution.*] Calculate the percentage of gabapentin related compound A in the portion of Gabapentin taken by the formula:

$$2500(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Gabapentin Related Compound A RS in the *Standard solution; W* is the amount, in mg, of Gabapentin taken to prepare the *Test solution*; r_i is the peak area of gabapentin related compound A in the *Test solution;* and r_S is the peak area of USP Gabapentin Related Compound A RS in the *Standard solution:* not more than 0.10% of gabapentin related compound A is found. Calculate the percentage of each impurity in the portion of Gabapentin taken by the formula:

$$2500(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Gabapentin RS in the *Standard solution; W* is the amount, in mg, of Gabapentin taken to prepare the *Test solution; r_i* is the peak area of any impurity different from gabapentin related compound A in the *Test solution;* and r_S is the peak area of USP Gabapentin RS in the *Standard solution:* not more than 0.10% of any individual impurity is found, and the sum of all impurities is not more than 0.50%.

Organic volatile impurities ⟨467⟩**:** meets the requirements.

Assay—

Diluent—Dissolve 2.32 g of ammonium phosphate monobasic in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Dissolve 0.58 g of ammonium phosphate monobasic and 1.83 g of sodium perchlorate in 1000 mL of water. Adjust with perchloric acid to a pH of 1.8.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (76 : 24). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Impurities solution—Dissolve suitable quantities of USP Gabapentin Related Compound A RS and USP Gabapentin Related Compound B RS in methanol to obtain a solution containing about 1.4 mg per mL and 0.84 mg per mL, respectively.

System suitability solution—Dissolve suitable quantities of USP Gabapentin RS in *Diluent,* and add an appropriate volume of *Impurities solution* to obtain a solution containing about 14.0 mg per mL, 0.014 mg per mL, and 0.0084 mg per mL of USP Gabapentin RS, USP Gabapentin Related Compound A RS, and USP Gabapentin Related Compound B RS, respectively.

Standard preparation—Dissolve accurately weighed quantities of USP Gabapentin RS and USP Gabapentin Related Compound E RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 14.0 mg per mL and 0.0084 mg per mL, respectively.

Assay preparation—Transfer about 350 mg of Gabapentin, 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 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. 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 2.75 for gabapentin related compound A, about 3.3 for gabapentin related compound B, and 1.0 for gabapentin; and the resolution, *R,* between gabapentin related compound A and gabapentin related compound B is not less than 2.3. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 2.7 for gabapentin related compound E and 1.0 for gabapentin; and the relative standard deviation for replicate injections is not more than 2.0% for the gabapentin 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 responses for the major peaks. Calculate the quantity, in mg, of $C_9H_{17}NO_2$ in the portion of Gabapentin taken by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Gabapentin 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.▲*USP29*

BRIEFING

Iodixanol, *USP 28* page 1039 and page 1908 of *PF* 29(6) [Nov.–Dec. 2003]. It is proposed to make a correction in the *Internal standard solution* in the test for *Limit of calcium*.

(PA5: A.Wilk) RTS—41999-1

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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.■1S (*USP28*)

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■1S (*USP28*)
USP Iodixanol RS. USP Iodixanol Related Compound C RS. USP Iodixanol Related Compound D RS. USP Iodixanol Related Compound E RS. USP Iohexol Related Compound B RS.

Change to read:

Limit of calcium—

Internal standard solution—Accurately weigh about 3.067 g of scandium oxide, and dissolve in 1 L of water (each mL contains ~~1.000 g~~

▲2.0 mg▲*USP29*
of scandium). Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Blank solution—Transfer 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix.

Standard solutions—Prepare a solution having a concentration of 10 µg of calcium per mL. Add 0.5, 2.5, 5.0, and 10.0 mL of this solution to separate 50-mL volumetric flasks. To each flask, add 5.0 mL of *Internal standard solution,* dilute with water to volume, and mix.

Test solution—Transfer about 2 g of Iodixanol, accurately weighed, to a 20-mL volumetric flask, add about 10 mL of water, and mix. Add 2.0 mL of *Internal standard solution,* dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of each *Standard solution* and the *Test solution* at 393.366 nm, the calcium emission line, and at 361.38 nm, the scandium emission line, with an atomic absorption spectrophotometer, using the *Blank solution* as the blank. Plot a standard curve of the ratio of the calcium absorption to the scandium absorption versus the respective calcium concentrations. From the graph so obtained, determine the calcium concentration, *C,* in µg per mL, in the *Test solution.* Calculate the content of calcium, in µg per g, in the portion of Iodixanol taken by the formula:

$$20(C/W),$$

in which C is as obtained above; and W is the weight, in g, of Iodixanol taken to prepare the *Test solution:* not more than 5 µg per g 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.*■1S (*USP28*)

BRIEFING

Levothyroxine Sodium Tablets, *USP 28* page 1128. It is proposed to add *Dissolution Test 3* to this monograph. The chromatographic procedure in this test was validated using a Discovery Cyano brand of column that contains L10 packing; a suitable alternative is the 4.6-mm × 7.5-cm Zorbax SB-CN brand of column that contains 3.5-µm packing. In the absence of any adverse comments, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of June 1, 2005.

(BPC: M. Marques) RTS—41612-1

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.]

▲▲*USP28*
TEST 1—

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl 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⟩).

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 *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.

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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.

•TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus, Time, Standard solution, and *Test solution*—Proceed as directed for *Test 1*. [NOTE—Filter the *Standard solution* in a manner identical to the *Test solution*.]

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 and acetonitrile (65 : 35) with 0.5 mL of phosphoric acid per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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 5-µm packing L10. The column temperature is maintained at 30°. 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 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 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.•[3]

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

▲NOTE—Do not use paddle stirrers with synthetic coating.▲*USP28*

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 *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.

BRIEFING

Loratadine Oral Solution, *USP 28* page 1150, the *Sixth Interim Revision Announcement* on page 1969 of *PF* 30(6) [Nov.–Dec. 2004], and page 2014 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to delete the *Antimicrobial effectiveness test.* This test is a formulation development and stability test, not a release test. Deletion of the *Antimicrobial effectiveness test* is consistent with other *USP* monographs for oral solutions.

(PA1: K. Russo; AMB: D. Porter) RTS—41936-1

Delete the following:

▲~~**Antimicrobial effectiveness test** ⟨51⟩**:** meets the requirements.~~▲*USP29*

Change to read:

Related compounds—

Mobile phase—Prepare a mixture of 15 mmol of 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⟩).

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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.

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.

■Allow to cool to room temperature, then dilute 5 mL with *Diluent* to 25 mL.■2S (*USP28*)

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 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 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%.

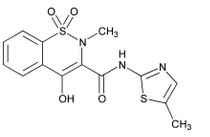
BRIEFING

Meloxicam. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The liquid chromatographic procedures in the *Related compounds Test 1* and in the *Assay* are based on analyses performed with the Inertsil ODS-2 brand of L1 column. The typical retention times for meloxicam are about 7 and 6 minutes for *Related compounds Test 1* and the *Assay,* respectively. The liquid chromatographic procedures in the *Related compounds Test 2* are based on analyses performed with the Purosphere RP-18e brand of L1 column. The typical retention time for meloxicam is about 5 minutes.

(PA2: D. Bempong; PSD: C. Okeke; NL: C. Barnstein) RTS—41206-1; 41637-1; 41689-1

Add the following:

▲Meloxicam



$C_{14}H_{13}N_3O_4S_2$ 351.40

4-Hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide [*71125-38-7*].

» Meloxicam contains not less than 99.0 percent and not more than 100.5 percent of $C_{14}H_{13}N_3O_4S_2$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

Labeling—The labeling states with which *Related compounds* test the article complies if a test other than *Test 1* is used.

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USP Reference standards ⟨11⟩—*USP Meloxicam RS. USP Meloxicam Related Compound A RS. USP Meloxicam Related Compound B RS. USP Meloxicam Related Compound C RS. USP Meloxicam Related Compound D RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩.

Spectral range: 240 to 450 nm.

Solution: 10 µg per mL.

Medium: methanol.

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%.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.001%.

Related compounds—[NOTE—Perform either *Test 1* or *Test 2* depending on the manufacturing process used.]

TEST 1—

Solution A: a 0.1% w/v solution of monobasic potassium phosphate adjusted with 1 N sodium hydroxide to a pH of 6.0.

Solution B: 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⟩).

System suitability solution—Transfer about 4 mg of USP Meloxicam RS and about 4 mg each of USP Meloxicam Related Compound A RS and USP Meloxicam Related Compound B RS into a 50-mL volumetric flask, dissolve in 5 mL of methanol and 0.3 mL of 1 N sodium hydroxide, dilute with methanol to volume, and mix.

Standard solution—Transfer about 12 mg of USP Meloxicam RS, accurately weighed, to a 20-mL volumetric flask, dissolve in 5 mL of methanol and 0.3 mL of 1 N sodium hydroxide, dilute with methanol to volume, and mix. Transfer 2 mL of this solution to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Test solution—Transfer about 80 mg of Meloxicam, accurately weighed, to a 20-mL volumetric flask, dissolve in 5 mL of methanol and 0.3 mL of 1 N sodium hydroxide, dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength or multi-wavelength UV detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 45°. The flow rate is about 1 mL per minute, and the detection wavelengths are 260 nm and 350 nm. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–2	60	40	isocratic
2–10	60→30	40→70	linear gradient
10–15	30	70	isocratic
15–15.1	30→60	70→40	linear gradient
15.1–18	60	40	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times based on the meloxicam peak at about 7 minutes are listed in *Table 1.* At 350 nm, the resolution, *R,* between meloxicam related compound A and meloxicam is not less than 3.0; at 260 nm, the resolution, *R,* between meloxicam related compound B and meloxicam is not less than 3.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms at detection wavelengths

of 260 nm and 350 nm, and measure the peak responses. Calculate the percentage of each impurity in the portion of Meloxicam taken by the formula:

$$100(C_S / C_T)(1 / F)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Meloxicam RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Meloxicam in the *Test solution; F* is the relative response factor (see *Table 1*); r_U is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of meloxicam at 350 nm obtained from the *Standard solution*. [NOTE—For the specified impurities, calculate the percentage content of each impurity, using the *Test solution* peak responses recorded at the detection wavelength given in *Table 1*. For an unknown impurity, calculate the percentage content, using peak responses recorded at the wavelength that gives the greater response.]

Table 1

Compound	Approximate Relative Retention Time	Wavelength (nm)	Relative Response Factor (*F*)	Limit (w/w, %)
4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid ethylester 1,1-dioxide (meloxicam related compound A)	1.4	350	0.5	0.1
2-Amino-5-methyl-thiazole (meloxicam related compound B)	0.4	260	1.0	0.1
4-Hydroxy-2-methyl-*N*-(*N*′-methyl-5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1, 1-dioxide	1.9	350	1.0	0.05
4-Hydroxy-2-methyl-*N*-(*N*′-ethyl-5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1, 1-dioxide	1.7	350	1.0	0.05
Individual unknown impurity	—	260/350	1.0	0.1
Total impurity	—	—	—	0.3

TEST 2—If an article complies with this test, the labeling indicates that it meets the requirements of *Related compounds Test 2*.

Solution A and *Solution B*—Prepare as directed in *Test 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: a mixture of *Diluent B* and 0.4 N sodium hydroxide (50 : 3).

Diluent B: a mixture of water and methanol (60 : 40).

Standard stock solution 1—Prepare a solution having a known concentration of about 50 µg per mL of USP Meloxicam RS in *Diluent A*. Transfer 2 mL of the solution to a 10-mL volumetric flask, dilute with *Diluent B* to volume, and mix.

Standard stock solution 2—Transfer about 5 mg each of USP Meloxicam Related Compound B RS, USP Meloxicam Related Compound C RS, and USP Meloxicam Related Compound D RS into a 100-mL volumetric flask, add 6 mL of 0.4 N sodium hydroxide, and sonicate for about 2 minutes. Add 40 mL of methanol to the resulting solution, sonicate for about 2 minutes, dilute with water to volume, and mix.

Standard solution—Transfer 1 mL each of *Standard stock solution 1* and *Standard stock solution 2* into a 10-mL volumetric flask, dilute with *Diluent B* to volume, and mix.

System suitability stock solution—Prepare a solution containing about 2 mg per mL of USP Meloxicam RS in *Diluent A*.

System suitability solution—Transfer 5 mL of *System suitability stock solution* and 1 mL of *Standard stock solution 2* into a 10-mL volumetric flask, dilute with *Diluent B* to volume, and mix.

Test solution—Transfer about 20 mg of Meloxicam, accurately weighed, to a 20-mL volumetric flask, dissolve in 10 mL of *Diluent A,* dilute with *Diluent B* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength or multi-wavelength UV detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 45°. The flow rate is about 1 mL per minute and the detection wavelengths are 260 nm and 350 nm. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	45	55	isocratic
25–30	45→30	55→70	linear gradient
30–40	30	70	isocratic
40–45	30→45	70→55	linear gradient
45–50	45	55	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times based on the meloxicam peak at about 5 minutes are listed in *Table 2;* and the resolution, *R,* between meloxicam related compound D and meloxicam at 350 nm is not less than 5.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0% for meloxicam related compound C and for meloxicam related compound D at 350 nm; and not more than 5.0% for meloxicam related compound B at 260 nm.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms at detection wavelengths of 260 nm and 350 nm, and measure the peak responses. Calculate the percentage of each impurity in the portion of Meloxicam 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 the corresponding USP Related Compound RS in the *Standard solution* [NOTE—Use the concentration of the USP Meloxicam RS for unknown impurities.]; C_T is the concentration, in mg per mL, of Meloxicam in the *Test solution;* r_U is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of the corresponding related

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compound obtained from the *Standard solution.* [NOTES—Use the peak response of the USP Meloxicam RS for unknown impurities; for the specified impurities, calculate the percentage content of each impurity using the *Test solution* peak responses recorded at the detection wavelength given in *Table 2.* For an unknown impurity, calculate the percentage content using peak responses recorded at the wavelength that gives the greater response.]

Table 2

Compound	Approximate Relative Retention Time	Wavelength (nm)	Limit (w/w, %)
2-Amino-5-methyl-thiazole (meloxicam related compound B)	0.8	260	0.1
Isopropyl-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (meloxicam related compound C)	3.2	350	0.1
4-Methoxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2yl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam related compound D)	2.4	350	0.1
Individual unknown impurity	—	260/350	0.1
Total impurity	—	—	0.3

Assay—

Buffer solution: a mixture of 0.1% w/v solution of ammonium acetate adjusted with 10% ammonia solution to a pH of 9.1.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (58 : 42). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 4 mg of USP Meloxicam RS and about 4 mg of USP Meloxicam Related Compound A RS into a 50-mL volumetric flask, dissolve with 25 mL methanol and 0.1 mL of 1 N sodium hydroxide, dilute with water to volume, and mix.

Standard preparation—Transfer about 20 mg of USP Meloxicam RS, accurately weighed, into a 100-mL volumetric flask, dissolve in 50 mL of methanol and 0.2 mL of 1 N sodium hydroxide, dilute with water to volume, and mix.

Assay preparation—Transfer about 20 mg of Meloxicam, accurately weighed, into a 100-mL volumetric flask, dissolve in 50 mL of methanol and 0.2 mL of 1 N sodium hydroxide, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 360-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The column temperature is maintained at 45°. 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 0.7 for related compound A and 1.0 for meloxicam; the resolu-

tion, *R,* between the two peaks is not less 3.0; the tailing factor for the meloxicam peak is not more than 2.0; and the relative standard deviation for replicate injections, calculated for the meloxicam peak, 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 meloxicam peak. Calculate the quantity, in mg, of $C_{14}H_{13}N_3O_4S_2$ in the portion of Meloxicam taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Meloxicam 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.▲*USP29*

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 (*USP28*)

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■1S (*USP28*)
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.*■1S (*USP28*)

BRIEFING

Meperidine Hydrochloride, *USP 28* page 1208 and page 1924 of *PF* 29(6) [Nov.–Dec. 2003]. This monograph has been revised in accordance with the new *Guidelines for Packaging and Storage Statements in USP–NF Monographs* under *General Notices and Requirements* for active pharmaceutical ingredients (APIs) published in *PF* 30(3) [May–June 2004] on page 801.

(PA2: C. Anthony; PSD: C. Okeke) RTS—40352-1

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers, ~~Store at 25°, excursions permitted between 15° and 30°.~~

▲and store at room temperature.▲*USP29*

BRIEFING

Metformin Hydrochloride, *USP 28* page 1231 and page 1925 of *PF* 29(6) [Nov.–Dec. 2003]. It is proposed to revise the *Packaging and storage* section that was originally proposed for this monograph in *PF* 29(6).

(PA4: E. Gonikberg; PSD: C.Okeke) RTS— 40988-1

Add the following:

▲**Packaging and storage**—Preserve in well-closed containers. ~~Store at 25°, excursions permitted between 15° and 30°.~~ Store at room temperature.▲*USP29*

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BRIEFING

Methenamine Hippurate Tablets, *USP 28* page 1242. It is proposed to add a *Dissolution Test 2* in this monograph for the generic versions of this product.

(BPC: M. Marques) RTS—40621-3

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.▲*USP29*

Change to read:

Dissolution ⟨711⟩**—**

▲TEST 1—▲*USP29*

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.

▲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: 60 minutes.

Standard solution and *Procedure*—Proceed as directed under *Test 1*.

Tolerances —Not less than 80% *(Q)* of the labeled amount of $C_6H_{12}N_4 \cdot C_9H_9NO_3$ is dissolved in 60 minutes.▲*USP29*

BRIEFING

Nabumetone, *USP 28* page 1320. On the basis of comments received, it is proposed to revise the *Related compounds* test to provide the names of the related compounds.

(PA2: D. Bempong) RTS—41890-1

Change to read:

Related compounds—
Solution A, Solution B, and *Mobile phase*—Proceed as directed in the *Assay.*
System suitability solution—Dissolve accurately weighed quantities of USP Nabumetone RS and USP Nabumetone Related Compound A RS in acetonitrile to obtain a solution having known concentrations of about 1 mg per mL and 1 µg per mL, respectively.
Test solution—Use the *Assay preparation*.
Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for nabumetone related compound A and 1.0 for nabumetone; the resolution, *R,* between nabumetone related compound A and nabumetone is not less than 1.5; the column efficiency is not less than 3600 theoretical plates; the tailing factor determined from the nabumetone peak is between 0.8 and 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.
Procedure—Inject 10 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 Nabumetone taken by the formula:

$$100Fr_i/(r_N + \Sigma Fr_i)$$

in which F is the relative response factor ~~and is equal to 0.12 for any peak with a relative retention time of 0.73, 0.10 for any peak with a relative retention time of 2.7, 0.25 for any peak with a relative retention time of 0.93, 0.42 for any peak with a relative retention time of 1.2, 0.94 for any peak with a relative retention time of 0.85, 1.02 for any peak with a relative retention time of 1.9, and 0.91 for any peak with a relative retention time of 2.6~~

▲for each impurity (see the accompanying table for values);▲*USP29*
r_i is the peak response for each impurity; and r_N is the nabumetone peak response. ~~not more than 0.3% of any impurity with a relative retention time of 2.7 is found; not more than 0.1% of any other individual impurity is found; and not more than 0.8% of total impurities is found~~

▲The limits of impurities are specified in the accompanying table.

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Compound	Approximate Relative Retention Time	Relative Response Factor	Limit (w/w, %)
Nabumetone	1.0	—	—
6-Methoxy-2-naphthaldehyde	0.73	0.12	0.1
4-(6′-Methoxy-2′-naphthyl)-butan-2-ol	0.85	0.94	0.1
1-(6′-Methoxy-2′-naphthyl)-but-1-en-3-one (nabumetone related compound A)	0.93	0.25	0.1
5-(6′-Methoxy-2′-naphthyl)-3-methylcyclohex-2-en-1-one	1.2	0.42	0.1
5-(6′-Methoxy-2′-naphthyl)-3-methylcyclohexan-1-one	1.9	1.02	0.1
1,5-Di-(6′-methoxy-2′-naphthyl)-pentan-3-one	2.6	0.91	0.1
6,6-Dimethoxy-2,2′-binaphthyl	2.7	0.10	0.3
Individual unknown impurity	—	—	0.1
Total impurity	—	—	0.8

▲*USP29*

BRIEFING

Oxandrolone, *USP 28* page 1426 and page 148 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to replace the liquid chromatographic procedure in the test for *Related compounds* with a linear gradient elution method that provides greater sensitivity to the impurities and makes the method stability indicating. The previously proposed revision to the test for *Related compounds,* which appeared in *PF* 30(1), is being canceled. It is also proposed to further revise the *Assay* to make additional modifications to the *Mobile phase, Standard preparation, Chromatographic system,* and *Procedure*.

(PA1: C. Anthony) RTS—41280-1

Change to read:

» Oxandrolone contains not less than ~~97.0~~ ■98.0■1S (*USP28*) percent and not more than ~~100.5~~ ■102.0■1S (*USP28*) percent of $C_{19}H_{30}O_3$, calculated on the dried basis.

Change to read:

USP Reference standards ⟨11⟩—*USP Oxandrolone RS.* ▲*USP Oxandrolone Related Compound A RS. USP Oxandrolone Related Compound B RS. USP Oxandrolone Related Compound C RS.*▲*USP29*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: ~~Prepare a solution in chloroform containing 5 mg per mL. Apply 10 µL each of this solution and a solution of USP Oxandrolone RS in chloroform, containing 5 mg per mL 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 in a solvent system consisting of a mixture of chloroform and methanol (19 : 1) 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 dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_F value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.~~

In-Process Revision

■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 (*USP28*)

Delete the following:

~~■**Ordinary impurities** ⟨466⟩—~~
~~*Test solution:* — methanol.~~
~~*Standard solution:* — methanol.~~
~~*Application volume:* — 10 µL.~~
~~*Eluant:* — a mixture of toluene and isopropyl alcohol (90 : 10), in a nonequilibrated chamber.~~
~~*Visualization:* — 5.~~ ■1S (*USP28*)

Add the following:

▲**Related compounds**—

Solution A: acetonitrile.

Solution B: 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 1—Weigh accurately 5 mg of USP Oxandrolone Related Compound A RS and 5 mg of USP Oxandrolone Related Compound C RS into a 50-mL volumetric flask, dissolve in 25 mL of acetonitrile using an ultrasonic bath, dilute with acetonitrile to volume, and mix.

Standard solution 2—Weigh accurately 5 mg of USP Oxandrolone RS and 3 mg of USP Oxandrolone Related Compound B RS into a 25-mL volumetric flask, dissolve in 1 mL of acetonitrile, add 1.00 mL of *Standard solution 1,* dilute with acetonitrile to volume, and mix.

Standard solution 3—Dilute 1.0 mL of *Standard solution 2* with 4.0 mL of acetonitrile and 5.0 mL of water and mix.

Test solution—Weigh accurately 40 mg of Oxandrolone into a 10-mL volumetric flask, dissolve in 5.0 mL of acetonitrile using an ultrasonic bath, dilute with water to volume, and mix. [NOTE—*Test* and blank solutions are made up fresh and injected immediately.]

Chromatographic system—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1.The column temperature is maintained at 40°. The flow rate is about 0.7 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	equilibration
0–30	50→100	50→0	linear gradient
30–32	100→50	0→50	linear gradient
32–40	50	50	re-equilibration

Chromatograph *Standard solution 3,* and record the peak responses as directed for *Procedure*. The resolution, *R,* between oxandrolone related compound A and oxandrolone related compound B is not less than 1.5, and the resolution, *R,* between oxandrolone related compound B and oxandrolone is not less than 2.0; the tailing factor is not more than 1.1; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of *Standard solution 3* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of oxandrolone

related compound A and oxandrolone related compound C in the portion of Oxandrolone taken by the formula:

$$1000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of oxandrolone related compound A or oxandrolone related compound C in *Standard solution 3; W* is the weight of Oxandrolone taken to prepare the *Test solution;* r_U is the peak area of oxandrolone related compound A or oxandrolone related compound C in the chromatogram of the *Test solution;* and r_S is the peak area obtained for oxandrolone related compound A or oxandrolone related compound C in the chromatogram of *Standard solution 3*.

Calculate the percentage of each impurity, other than oxandrolone related compound A and oxandrolone related compound C, by the formula:

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

in which F is the relative response factor for each impurity; C is the concentration, in mg per mL, of USP Oxandrolone RS in *Standard solution 3; W* is the weight of Oxandrolone taken to prepare the *Test solution;* r_U is the peak area of each impurity in the chromatogram of the *Test solution;* and r_S is the peak area obtained for oxandrolone in *Standard solution 3.* The impurities meet the requirements specified in the table below.

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
4-Oxa-isomer (17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one) Oxandrolone related compound B	0.94	0.73	0.3
Anhydro-oxandrolone (17β,17-dimethyl-2-oxa-18-nor–5α-androstan-3-one) Oxandrolone related compound C	3.29	—	0.5
Secodicarboxylic acid (17β-hydroxy-17α-methyl-2-nor-5α-androstan-1,3-dioic acid)	0.46	0.25	0.1
7,8-Didehydro-oxandrolone (17β-hydroxy-17α-methyl-2-oxa-5α-andrist-7-en-3-one) Oxandrolone related compound A	0.90	—	0.1
Oxandrolone open lactone methylester (methyl-(1,17β-dihydroxy-17α-methyl-1,3-seco-2-nor-5α-androstane-3-oate)	1.09	0.66	0.1
Secoacid anhydride (17β-hydroxy-17α-oxa-5α-androstan-1,3-dione)	1.12	0.40	0.1
Oxandrolone-17-acetate (17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one 17-acetate)	2.14	0.54	0.1
Unknown impurities	—	1.00	0.1
Total impurities	—	—	1.0

▲*USP29*

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Change to read:

Assay—~~Transfer about 500 mg of Oxandrolone, accurately weighed, to a 250-mL conical flask, and add 25.0 mL of 0.1 N alcoholic potassium hydroxide VS. Insert into the neck of the flask, by means of a perforated stopper, an air condenser consisting of a glass tube 70 to 80 cm in length and 5 to 8 mm in diameter, and heat the flask on a steam bath for 30 minutes, frequently rotating the contents. Cool, add 1 mL of phenolphthalein TS, and titrate the excess alkali with 0.1 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N alcoholic potassium hydroxide is equivalent to 30.64 mg of $C_{19}H_{30}O_3$.~~

▲*Mobile phase*—Prepare a filtered and degassed mixture of ~~0.01% (v/v) glacial acetic acid in~~ water and acetonitrile ~~(64 : 36)~~ (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Weigh accurately 30 mg of USP Oxandrolone RS into a 10-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Oxandrolone RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about ~~5~~ 3 mg per mL. [NOTE—Sonicate if necessary to dissolve.]

Assay preparation—Transfer to a suitable volumetric flask an accurately weighed quantity of Oxandrolone, and dissolve in and dilute with acetonitrile to volume to obtain a solution having a concentration of about ~~5~~ 3 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~198-nm~~ 210-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about ~~1.0~~ 0.8 mL per minute. Chromatograph the *Standard preparation* and the *System suitability 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 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about ~~25 µL~~ 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 $C_{19}H_{30}O_3$ taken by the formula:

$$VC(r_U / r_S),$$

in which V is the final volume, in ~~mg per~~ mL, of the *Assay preparation;* C is the concentration, in mg per mL, of USP Oxandrolone 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.▲*USP29*

BRIEFING

Oxandrolone Tablets, *USP 28* page 1427. It is proposed to replace the *Disintegration* test with a *Dissolution* test. The chromatographic procedure in the *Dissolution* test was validated using the RTX-5 brand of column containing packing G27. In the absence of any adverse comment, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 28–NF 23*, with an official date of April 1, 2005.

(BPC: M. Marques) RTS—41372-1

Delete the following:

•~~**Disintegration** ⟨701⟩: 15 minutes.~~•[2]

Add the following:

•**Dissolution** ⟨711⟩—

Medium: a solution of water and isopropanol (7 : 3); 500 mL.

Apparatus 2: 100 rpm.

Time: 60 minutes.

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Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Internal standard solution—Dissolve accurately weighed quantities of 17α-methyl testosterone, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.2 mg per mL (for tablets with 2.5-mg label claim) and about 0.8 mg per mL (for tablets with 10-mg label claim).

Standard solution—Dissolve an accurately weighed quantity of USP Oxandrolone RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 1 mg per mL.

Working standard solution—Combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polytef filter. Transfer 20 mL of the filtrate to a separatory funnel, add 400 µL of the *Internal standard solution,* 40 mL of 10% potassium chloride solution, and 8 mL of chloroform. In separate separatory funnels, prepare an extraction blank and an internal standard blank in a similar manner using 20 mL of filtered *Medium* in place of the solution under test and excluding the *Internal standard solution* from the extraction blank. Shake each funnel, and allow the layers to separate. Collect the lower chloroform layer. Repeat the extraction procedure one more time. Evaporate the solvents under a stream of nitrogen at 45° until just dry. Reconstitute the dried residue with 2 mL of acetonitrile (for tablets with 2.5-mg label claim) or with 8 mL of acetonitrile (for tablets with 10-mg label claim), and sonicate for 10 minutes.

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 0.5-µm phase G27. The carrier gas is helium, flowing at a rate of about 16.8 mL per minute. The injection port and detector temperatures are maintained at 190° and 320°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is increased at a rate of 25° per minute to 280°, and maintained at 280° for 3 minutes. Then the column temperature is increased at a rate of 10° per minute to 320°, and maintained at 320° for 3 minutes. Chromatograph the acetonitrile, the extraction blank, and the internal standard blank, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5. Make two injections of the *Working standard solution,* and record the peak responses. The average oxandrolone/*Internal standard solution* peak area percent comparison is between 98.0% and 102.0%. The resolution between the oxandrolone peak and the nearest eluting peak is equal to or greater than 1.5.

Procedure—Separately inject equal volumes (0.5 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 $C_{19}H_{30}O_3$ released by the formula:

$$\frac{C_s \times \text{sample ratio} \times V_{UF} \times 500 \times 100}{\text{Standard ratio} \times V_{UI} \times LC},$$

in which C_S is the concentration, in mg per mL, of oxandrolone in the *Standard solution;* sample ratio is the area ratio of oxandrolone to 17α-methyltestosterone in the sample injection for each *Test solution;* V_{UF} is the final volume, in mL, of the sample after reconstitution of the dry residue; 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; standard ratio is the mean area ratio of oxandrolone to 17α-methyltestosterone in all injections of the

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Standard solution; V_{UI} is the initial sample volume, in mL, used in the extraction; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of oxandrolone ($C_{19}H_{30}O_3$) is dissolved in 60 minutes.●2

BRIEFING

Paroxetine Hydrochloride *USP 28* page 1474 and page 1282 of *PF* 30(4) [Jul.–Aug. 2004]. It is proposed to replace the method in the test for *Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine* with a validated test that does not use a tandem mass spectrophotometric detector. The proposed method was validated using a Purospher RP-18e brand of L1 column. The retention time of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine is about 20 minutes. In addition, in the test for *Chromatographic purity* it is proposed to replace USP Paroxetine Related Compound A RS and USP Paroxetine Related Compound B RS with USP Paroxetine Hydrochloride for System Suitability RS in the *System suitability solution* section under *Test 1.*

(PA3: S. Salado) RTS—40496-1; 41807-1

Change to read:

Packaging and storage—Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in well-closed containers. ~~Store between 15° and 30°.~~

■Store at controlled room temperature.■1S *(USP28)*

Change to read:

USP Reference standards ⟨11⟩**—***USP Paroxetine Hydrochloride RS.* ~~USP Paroxetine Related Compound A RS.~~

▲*USP Paroxetine Hydrochloride for System Suitability RS.*▲*USP29*
USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS. USP Paroxetine Related Compound E RS. USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.

Change to read:

Water, *Method I* ⟨921⟩**:** not more than ~~1.0%~~

■1.5%■1S *(USP28)*
for the anhydrous form and between 2.2% and 2.8% for the hemihydrate form.

Change to read:

Limit of related compound C—
Mobile phase—Prepare a mixture of *n*-hexane,

■absolute■1S *(USP28)*
alcohol, water, and trifluoroacetic acid (900 : 100 : 2 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Diluent: a mixture of

■absolute■1S *(USP28)*
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 Paroxetine Hydrochloride 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 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 are 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.~~

■2.5.■1S *(USP28)*
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 responses for the major peaks. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

$$2500(C/W)(r_i / r_S),$$

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 obtained from the *Test solution* and the *Standard solution,* respectively: not more than of 0.1% of paroxetine related compound C is found.

Change to read:

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⟩).~~

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~~*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 100 ng per mL.~~

~~■20 ng per mL.■ IS (USP23).~~

~~*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 dissociation 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 responses for the major peaks. Calculate the amount, in 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, 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 20 ng is found (0.0001%).~~

▲*Solution A*—Dissolve about 30 g of sodium perchlorate in about 900 mL of water. Add 3.5 mL of phosphoric acid and 2.4 mL of triethylamine. Dilute with water to volume, and mix. Adjust with phosphoric acid or triethylamine to a pH of 2.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution B: acetonitrile, filtered and degassed.

Diluent: a mixture of water and acetonitrile (4 : 1).

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 solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride Related Compound E RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 42 ng per mL of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine.

Test solution—Transfer about 420 mg of Paroxetine Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve in about 7 mL of *Diluent* with sonication. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 242-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	85	15	equilibration
0–20	85→80	15→20	linear gradient
20–27	80→55	20→45	linear gradient
27–36	55	45	isocratic
36–38	55→80	45→15	linear gradient
38–45	85	15	re-equilibration

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative retention times are 0.6 for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine and 1.0 for paroxetine; and the relative standard deviation for replicate injections is not more than 15.0% for the 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine peak.

In-Process Revision

Procedure—Separately inject equal volumes (about 75 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 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$1000(CI/W)\ (r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride Related Compound E RS in the *Standard solution; I* is the fraction, by weight, of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in USP Paroxetine Hydrochloride Related Compound E RS; 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 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine obtained from the *Test solution* and the *Standard solution,* respectively: not more than of 0.0001% of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine is found.▲*USP29*

Change to read:

Chromatographic purity—[NOTE—Perform 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 *Diluent* to obtain a solution having known concentrations of about 0.01 mg of each USP Reference Standard per mL.~~

▲Dissolve, by sonication if necessary, a suitable quantity of USP Paroxetine Hydrochloride for System Suitability RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.▲*USP29*

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in 20 mL of *Diluent,* sonicate, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector 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 relative retention times are about ~~1.1 for paroxetine related compound B, and 1.0 for paroxetine related compound A~~

▲0.66 for paroxetine related compound A, 0.73 for paroxetine related compound B, and 1.0 for paroxetine;▲*USP29* 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; 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,* the *Test solution,* and the *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 from the chromatogram of the *Diluent;* and r_S is the peak area of paroxetine obtained from the *Standard solution:* not more than of 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 L 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 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 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.

BRIEFING

Pentobarbital, *USP 28* page 1507 and page 154 of *PF* 30(1) [Jan.–Feb. 2004]; **Pentobarbital Sodium,** *USP 28* page 1509 and page 157 of *PF* 30(1) [Jan.–Feb. 2004]. According to the data received, when the material is intended for veterinary use, the approved limit of the known impurity, 5-ethyl-5-(1-ethylpropyl) barbituric acid, commonly known as the 3-isomer is 3%. Hence, it is proposed to change the assay limits from 98.0%–102.0% to 97.0%–102.0% .

(PA3: R. Ravichandran) RTS—41978-1

Change to read:

» Pentobarbital contains not less than ▲98.0▲*USP28* percent and not more than ▲102.0▲*USP28* percent of $C_{11}H_{18}N_2O_3$, calculated on the dried basis.

▲Where the material is labeled as intended solely for veterinary use, Pentobarbital contains not less than 97.0 percent and not more than 102.0 percent of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis.▲*USP29*

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. Pentobarbital intended for veterinary use only is so labeled.■2S *(USP28)*

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S *(USP28)*
USP Pentobarbital RS.

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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 (*USP28*)

BRIEFING

Pentobarbital Sodium, *USP 28* page 1509 and page 157 of *PF* 30(1) [Jan.–Feb. 2004]—See briefing under *Pentobarbital*.

(PA3: R. Ravichandran) RTS—41978-2

Change to read:

» Pentobarbital Sodium contains not less than ▲98.0▲*USP28* percent and not more than ▲102.0▲*USP28* percent of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis.

▲Where the material is labeled as intended solely for veterinary use, Pentobarbital Sodium contains not less than 97.0 percent and not more than 102.0 percent of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis.▲*USP29*

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. Pentobarbital Sodium intended for veterinary use only is so labeled.■2S (*USP28*)

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS*.■2S (*USP28*)
USP Pentobarbital RS.

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 (*USP28*)

BRIEFING

Scopolamine Hydrobromide, *USP 28* page 1756. It is proposed to revise *Identification* test *A* to eliminate the use of ethyl ether and to improve the robustness of the sample preparation.

(PA6: L. Evans) RTS—41829-1

Change to read:

Identification—

A:

▲*Infrared Absorption* ⟨197K⟩—▲*USP29*

~~Dissolve 3 mg in 1 mL of alcohol, and evaporate the solution on a steam bath to dryness. Dissolve the residue in 0.5 mL of chloroform, add 200 mg of potassium bromide and 15 mL of ether, and stir frequently during 5 minutes. Decant the solvent, dry the residue on a steam bath until the odor of the solvent no longer is perceptible, and compress the residue to a disk: the IR absorption spectrum of the resulting potassium bromide dispersion, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Scopolamine Hydrobromide RS, treated in the same manner~~

▲*Test specimen*—Dissolve 3 mg in 1 mL of alcohol, and evaporate the solution on a steam bath to dryness. Dissolve the residue in 0.5 mL of chloroform, add 200 mg of potas-

In-Process Revision

sium bromide, previously dried at 105° for 30 minutes, and stir frequently for 5 minutes. Allow the chloroform to evaporate to dryness and stir frequently to obtain a flowing powder residue. Dry the residue on a steam bath for 5 minutes, then immediately compress the residue to a disk.▲*USP29*

B: To 1 mL of a solution (1 in 20) add a few drops of chlorine TS, and shake the mixture with 1 mL of chloroform: the latter assumes a brownish color.

BRIEFING

Spironolactone Tablets, *USP 28* page 1800. It is proposed to revise the *Assay* to improve its applicability to various dosage amounts.

(PA5: A. Wilk) RTS—41976-1

Change to read:

Assay—

Mobile phase, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Spironolactone*.

▲*Diluent*—Prepare a mixture of acetonitrile and water (1 : 1).▲*USP29*

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 500 mL of acetonitrile, shake for 30 minutes, and then sonicate for an additional 30 minutes. Cool to room temperature, dilute with water 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 (1 : 1) to obtain a solution having a concentration of 0.5 mg of spironolactone per mL.~~

▲Accurately weigh not fewer than 10 Tablets, and transfer to a suitable volumetric flask. [NOTE—The target concentration is about 1 mg per mL.] Add a sufficient quantity of *Diluent,* shake for about 30 minutes, and sonicate for 30 minutes or until the Tablets are disintegrated. Cool the solution to room temperature, dilute with *Diluent* to volume, and centrifuge a suitable portion of the mixture. Quantitatively dilute a portion of this solution with *Diluent* to obtain a solution having a known concentration of about 0.5 mg of spironolactone per mL.▲*USP29*

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Spironolactone.* Calculate the quantity, in mg, of spironolactone ($C_{24}H_{32}O_4S$) in the portion of Tablets taken by the formula:

~~$50C(r_U/r_S)$,~~

▲$CD(r_U/r_S)$,▲*USP29*

in which C is the concentration, in mg per mL, of USP Spironolactone RS in the *Standard preparation;*

▲D is the dilution factor for the *Assay preparation;*▲*USP29* and r_U and r_S are the peak responses for spironolactone obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Succinylcholine Chloride, *USP 28* page 1807. It is proposed to revise the procedure for *Chromatographic purity, Test 2 (Limit of choline)* to correct the concentration of sodium chloride in the *System suitability solution*. Because this test was developed and validated specifically for the quantitation of choline, it is also proposed that the *Procedure* be revised to remove the formula for calculating the percentage of any other unknown impurities.

(PA1: K. Russo) RTS—41717-1

Change to read:

Chromatographic purity—

TEST 1—

Buffer solution—Prepare a solution in water containing 3.85 g per L of 1-pentanesulfonic acid, 2.9 g per L 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.

In-Process Revision

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, if present (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 Succinylmonocholine 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 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~~

▲0.01▲*USP29*
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 suitable device for chemical suppression, 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 uses a suitable regenerant flow rate 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 the *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:*~~

▲and▲*USP29*
not more than 1.5% of total impurities is found, the results for *Test 1* and *Test 2* being added.

BRIEFING

Terbutaline Sulfate, *USP 28* page 1869 and page 1585 of *PF* 29(5) [Sept.–Oct. 2003]; **Terbutaline Sulfate Tablets,** *USP 28* page 1871 and page 188 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to change the name of USP Terbutaline Sulfate Related Compound A RS to USP Terbutaline Related Compound A RS, in accordance with the current naming conventions.

(PA1: K. Russo) RTS—42028-1

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 *(USP28)*

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP28*)
USP Terbutaline Sulfate RS. ~~*USP Terbutaline Sulfate Related Compound A RS*~~

▲*USP Terbutaline Related Compound A RS.*▲*USP29*

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 (*USP28*)

BRIEFING

Terbutaline Sulfate Tablets, *USP 28* page 1871 and page 188 of *PF* 30(1) [Jan.–Feb. 2004]—See briefing under *Terbutaline Sulfate*.

(PA1: K. Russo) RTS—42028-2

Change to read:

USP Reference standards ⟨11⟩—*USP Terbutaline Sulfate RS.* ~~*USP Terbutaline Sulfate Related Compound A RS*~~

▲*USP Terbutaline Related Compound A RS.*▲*USP29*

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

■■2S (*USP28*)
⟨711⟩—
Medium: water; 900 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure—

■Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.■2S (*USP28*)

Determine the amount of $(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$ dissolved, employing the procedure set forth in the *Assay,* making any necessary modifications.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$ is dissolved in 45 minutes:

■the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q,* is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

■2S (*USP28*)

In-Process Revision

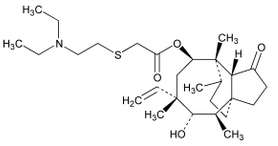
BRIEFING

Tiamulin. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The gas chromatographic procedure in the test for *Limit of alcohol and toluene* is based upon analyses performed with the HP-INNOWax brand of 530-µm × 30-m column coated with a 1.0-µm film of phase G16. In the test for *Related compounds* and the *Assay,* the Supelcosil LC-18-DB and Polaris C18-A brands of 4.6-mm × 15-cm column containing 5-µm L1 packing are suitable. Interested parties are encouraged to submit comments to the USP Veterinary Drugs Expert Committee.

(VET: I. DeVeau) RTS— 41731-1; 41731-2

Add the following:

▲Tiamulin



$C_{28}H_{47}NO_4S$ 493.74

Acetic acid, [[2-(diethylamino)ethyl]thio]-, 6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester [3a*S*-(3aα,4*β*,5α,6α,8*β*,9α,9a*β*,10*S**)].

[[2-(Diethylamino)ethyl]thio]acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10)-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one [*55297-95-5*].

» Tiamulin contains not less than 96.5 percent and not more than 102.0 percent of $C_{28}H_{47}NO_4S$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers, and store at room temperature.

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

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Tiamulin RS. USP Tiamulin Fumarate RS.*

Clarity and color of solution—Dissolve 2.5 g in methanol, and dilute with methanol to 50.0 mL. Solution is clear and its absorbance at 420 nm is not more than 0.050 (see *Spectrophotometry and Light-Scattering* ⟨851⟩).

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the tiamulin 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 0.4 USP Endotoxin Units per mg.

Loss on drying ⟨731⟩**—**Dry it at about 80° to constant weight: it loses not more than 1.0% of its weight.

Limit of alcohol and toluene—

Internal standard solution—To a 100-mL volumetric flask add about 90 mL of dimethylformamide and 150 µL of dioxane, dilute with dimethylformamide to volume, and mix.

Standard solution—To a 50-mL volumetric flask add about 40 mL of *Internal standard solution,* 100 µL of dehydrated alcohol, and 10 µL of toluene. Dilute with *Internal standard solution* to volume, and mix. Transfer 2 mL of this solution to a 20-mL headspace vial.

Test solution—Transfer about 200 mg of Tiamulin, accurately weighed, to a 20-mL headspace vial. Add 2 mL of *Internal standard solution,* close the vial, and sonicate to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.530-mm × 30-m capillary column coated with a 1.0-µm film of phase G16 and operated in 1/10 split mode. The carrier gas is helium flowing at a rate of about 30 mL per minute. The vial is heated to 100°, the injector syringe is heated to 130°, the injector port temperature is maintained at 200°, and the detector temperature is maintained at 250°. The column temperature is programmed to be isothermal at 50° for 8 minutes followed by a linear increase of 40° per minute until the temperature has reached 150°. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.5, 0.9, and 1.0 for alcohol, toluene, and dioxane, respectively; the resolution, *R,* between toluene and dioxane is not less than 2.0; the tailing factor of toluene and alcohol is not more than 2.0; and the relative standard deviation for triplicate injections, calculated from the ratio between the toluene or alcohol peak relative to the internal standard peak, is not more than 5.0%.

Procedure—Separately inject equal volumes (about 1.0 mL) of the headspace of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for alcohol, toluene, and dioxane. Calculate the percentages (w/w) of alcohol and toluene in the portion of Tiamulin taken by the formula:

$$0.04P(DV/W_U)(R_U/R_S),$$

in which P is the percent purity of the solvent of interest in the *Standard solution; D* is the density, in mg per mL, of the solvent of interest used to prepare the *Standard solution; V* is the volume, in mL, of the solvent of interest used to prepare the *Standard solution;* W_U is the weight, in mg, of Tiamulin taken to prepare the *Test solution;* and R_U and R_S are the peak response ratios of the solvents of interest obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.0% of alcohol is found, not more than 0.08 % of toluene is found, and not more than 1.0% of alcohol plus toluene is found.

Related compounds—

Ammonium carbonate buffer, Mobile phase, and *Diluent*—Proceed as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Toluene solution—Transfer 0.1 mL of toluene to a 100-mL volumetric flask, dilute with acetonitrile to volume, and mix. Transfer 0.1 mL of this solution to another 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution 1—Use the *Assay preparation.*

Test solution 2—Add 1.0 mL of *Test solution 1* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the retention times of possible tiamulin-related impurities relative to tiamulin are about 0.22 for mutilin, 0.50 for 2-(benzylsulfanyl)-*N*,*N*-diethylethanamine, 0.66 for 2,2′-(disulfane-1,2-diyl)-bis(*N*,*N*-diethylethanamine), 1.1 for hydroxy-11-oxotiamulin, 1.6 for 1-hydroxy-11-oxotiamulin, and 2.4 for 11-oxotiamulin. [NOTE—Impurities are not limited to those listed above.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution, Toluene solution, Test solution 1,* and *Test solution 2* into the chromatograph, record the chromatograms, identify the peaks, and measure the areas for the major peaks. Disregarding the toluene peak and any peak in the chromatogram of *Test solution 1* less than 0.1 times the area of the principal peak in the chromatogram

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obtained with *Test solution 2,* calculate the area percentage of each impurity, relative to tiamulin, in the portion of Tiamulin taken by the formula:

$$(r_i / r_S),$$

in which r_i is the peak area of each individual impurity obtained from *Test solution 1;* and r_S is the peak area of Tiamulin obtained from *Test solution 2:* not more than 1.0% of any identified impurity is found; not more than 0.2% of any unidentified impurity is found; and not more than 3.0% of total impurities is found.

Assay—

Ammonium carbonate buffer—Dissolve 10.0 g of ammonium carbonate in water, add 22 mL of perchloric acid TS, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 10.0.

Mobile phase—Mix 490 mL of methanol, 300 mL of *Ammonium carbonate buffer,* and 210 mL of acetonitrile.

Diluent—Mix 500 mL of *Ammonium carbonate buffer* and 500 mL of acetonitrile.

Standard preparation—Dissolve an accurately weighed quantity of USP Tiamulin Fumarate RS in *Diluent* to obtain a solution having a known concentration of about 5.0 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Tiamulin in *Diluent* to obtain a solution having a known concentration of about 4.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 212-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. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between tiamulin and its subsequent peak is not less than 2.

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 $C_{28}H_{47}NO_4S$ in the portion of Tiamulin taken by the formula:

$$P(C_S / C_U)(r_U / r_S),$$

in which P is the labeled percentage of tiamulin of USP Tiamulin Fumarate RS; C_S and C_U are the concentrations, in mg per mL, of the *Standard preparation* and *Assay preparation,* respectively; and r_U and r_S are the peak areas of tiamulin obtained from the *Assay preparation* and *Standard preparation,* respectively.▲*USP29*

BRIEFING

Ursodiol Capsules, *USP 28* page 2006. It is proposed to correct the molar concentration of the dissolution *Medium*.

(BPC: M. Marques) RTS—41828-1

Change to read:

Dissolution ⟨711⟩—
Medium: ~~0.2 M~~

▲0.5 M▲*USP29*
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 ($C_{24}H_{40}O_4$) 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⟩).

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Standard solution—Dissolve an accurately weighed quantity of USP Ursodiol RS, and dilute quantitatively, and stepwise if necessary, with *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.

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 and detector temperatures are maintained at 40°. 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.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{40}O_4$ is dissolved in 30 minutes.

BRIEFING

Zinc Oxide, *USP 28* page 2054. It is proposed to revise the test for *Iron and other heavy metals* to provide more clarity to the procedure.

(PA6: L. Evans) RTS—41908-1

Change to read:

Iron and other heavy metals~~— Cooled 5-mL portions of the solution obtained in the test for *Carbonate and color of solution* yield white precipitates with potassium ferrocyanide TS and with sodium sulfide TS.~~

▲Cool two separate 5-mL portions of the solution obtained in the test for *Carbonate and color of solution.* White precipitates are formed when potassium ferrocyanide TS is added to the first portion and when sodium sulfide TS is added to the second portion.▲*USP29*

BRIEFING

Zinc Oxide Neutral. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(DSN: L. Evans; PSD: C. Okeke; NL: C. Barnstein) RTS—34758-1; 39969-1; 39969-2; 40131-1; 41305-1; 41568-1

Add the following:

▲Zinc Oxide Neutral

ZnO 81.39

» Zinc Oxide Neutral, freshly ignited, contains not less than 95.0 percent and not more than 98.0 percent of ZnO.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Labeling—Label it to indicate that it is for use in sunscreen preparations only.

Identification—

A: When strongly heated, it assumes a yellow color that disappears on cooling.

B: A solution of it in a slight excess of 3 N hydrochloric acid responds to the tests for *Zinc* ⟨191⟩.

Alkalinity—Mix 1.0 g with 10 mL of hot water. The addition of two drops of phenolphthalein TS produces no color change.

Loss on ignition ⟨733⟩**—**Weigh accurately about 1 g, and ignite at 750° for 15 minutes: it loses not more than 5.0% of its weight.

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Carbonate and color of solution—Mix 2.0 g with 10 mL of water, add 30 mL of 2 N sulfuric acid, and heat on a steam bath with constant stirring: no effervescence occurs, and the resulting solution is clear and colorless. [NOTE—Use this solution in the test for *Iron and other heavy metals.*]

Sulfate ⟨221⟩**—**A 0.1 g portion shows no more sulfate than corresponds to 2.3 mL of 0.020 N sulfuric acid (2.2%).

Arsenic, *Method I* ⟨211⟩**:** 2 ppm.

Lead—Add 2 g to 20 mL of water, stir well, add 5 mL of glacial acetic acid, and warm on a steam bath until solution is effected: the addition of five drops of potassium chromate TS produces no turbidity or precipitate.

Mercury—

Mercury Detection Instrument and *Aeration Apparatus—*Proceed as directed for the section *Method IIa and Method IIb* under *Mercury* ⟨261⟩.

Nitric acid solution 1—Carefully add 50 mL of nitric acid to 450 mL of water, and mix.

Nitric acid solution 2—Carefully add 10 mL of nitric acid to 490 mL of water, and mix.

Hydrochloric acid–nitric acid solution—Carefully add three volumes of concentrated hydrochloric acid to one volume of concentrated nitric acid. [NOTE—Prepare immediately before use.]

Stannous sulfate solution—Add 25 g of stannous sulfate to 250 mL of 0.5 N sulfuric acid. [NOTE—The mixture is a suspension and should be stirred continuously during use.]

Sodium chloride–hydroxylamine sulfate solution—Dissolve 12 g of sodium chloride and 12 g of hydroxylamine sulfate in water, dilute with water to 100 mL, and mix.

Potassium permanganate solution—Dissolve 5 g of potassium permanganate in 100 mL of water, and mix.

Standard stock mercury solution—Dissolve 0.1354 g of mercuric chloride in *Nitric acid solution 1* to obtain a solution having a concentration of about 1.0 mg of mercury per mL. [NOTE—Use of a commercially prepared mercury standard is recommended.]

Standard working mercury solution—Quantitatively dilute an accurately measured volume of the *Standard stock mercury solution* with *Nitric acid solution 2* to obtain a solution having a known concentration of about 0.5 µg of mercury per mL.

Standard solutions—Transfer 1-, 2-, 3-, and 4-mL aliquots of *Standard stock mercury solution* to four separate 300-mL biological oxygen-demand (BOD) bottles. To each bottle, add 5 mL of water and 5 mL of *Hydrochloric acid–nitric acid solution*. Heat the sample for 2 minutes in a water bath at 95°. Cool, and add 50 mL of water and 15 mL of *Potassium permanganate solution*. Mix thoroughly, and place in a water bath for 30 minutes at 95°. Cool, add 5 mL of *Sodium chloride–hydroxylamine sulfate solution,* dilute with water to 200 mL, and mix. These solutions contain the equivalents of 2.5, 5, 7.5, and 10 ng of mercury per mL, respectively.

Blank solution—To a 300-mL BOD bottle, add 5 mL of water and 5 mL of *Hydrochloric acid–nitric acid solution*. Heat the solution for 2 minutes in a water bath at 95°. Cool, and add 50 mL of water and 15 mL of *Potassium permanganate solution*. Mix thoroughly, and place in a water bath for 30 minutes at 95°. Cool, add 5 mL of *Sodium chloride–hydroxylamine sulfate solution,* dilute with water to 200 mL, and mix.

Test solution—Transfer about 2.0 g of Zinc Oxide Neutral, accurately weighed, to a 300-mL BOD bottle. To the bottle, add 5 mL of water and 5 mL of *Hydrochloric acid–nitric acid solution*. Heat the sample in a water bath for 2 minutes at 95°. Cool, and add 50 mL of water and 15 mL of *Potas-*

sium permanganate solution. Mix thoroughly, and place in a water bath for 30 minutes at 95°. Cool, add 5 mL of *Sodium chloride–hydroxylamine sulfate solution,* dilute with water to 200 mL, and mix.

Procedure—Add 5 mL of *Stannous sulfate solution* to a *Standard solution,* and immediately insert the bottle into the *Aeration Apparatus*. Obtain the absorbance of the *Standard solution*. Repeat with the remaining *Standard solutions, Test solution,* and *Blank solution.* Perform a blank determination, and make any necessary corrections. Plot the absorbances of the *Standard solutions* versus concentrations, in µg per mL, and draw the straight line best fitting the plotted points. From the graph so obtained, determine the concentration, in µg per g of mercury, in the *Test solution*: not more than 1 µg per g is found.

Iron and other heavy metals—Cool two separate 5-mL portions of the solution obtained in the test for *Carbonate and color of solution*. White precipitates are formed when potassium ferrocyanide TS is added to the first portion and when sodium sulfide TS is added to the second portion.

Content of magnesium oxide—

Nitric acid solution—Carefully add 10 mL of concentrated nitric acid to 490 mL of water, and mix.

Standard solution—Prepare a solution in *Nitric acid solution* having a concentration of about 25 µg of magnesium per mL. [NOTE—Use of a commercially prepared magnesium–inductively coupled plasma standard solution is recommended.]

Test solution—Transfer 200 mg of Zinc Oxide Neutral, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Nitric acid solution* to volume.

Procedure—Set up an inductively coupled plasma–atomic emission spectrometer with a wavelength of 279.1 nm, RF power of about 1.2 KW, argon torch flow of about 17 L per minute, argon nebulizer flow of about 1.0 L per minute, and argon auxiliary flow of about 1.4 L per minute. Analyze the *Standard solution* and *Test solution,* using *Nitric acid solution* as the blank. Calculate the percentage of magnesium oxide in the portion of Zinc Oxide Neutral taken by the formula:

$$5F(C/W),$$

in which F is the conversion factor for conversion of magnesium to magnesium oxide (1.658); C is the concentration, in µg per mL, of magnesium found in the *Test solution,* determined from the instrument; and W is the weight, in mg, of the portion of Zinc Oxide Neutral taken to prepare the *Test solution*: not more than 0.7% is found.

Assay—Dissolve about 1.5 g of freshly ignited Zinc Oxide Neutral, accurately weighed, and 2.5 g of ammonium chloride in 50.0 mL of 1 N sulfuric acid VS, with the aid of gentle heat, if necessary. When dissolution is complete, add methyl orange TS, and titrate the excess sulfuric acid with 1 N sodium hydroxide VS. Each mL of 1 N sulfuric acid is equivalent to 40.69 mg of ZnO.▲*USP29*

BRIEFING

Zinc Sulfate Tablets. Because there is no existing *USP* monograph for this drug product, the following new monograph is being proposed. The development of this monograph has been requested by the United Nations International Children's Emergency Fund (UNICEF), the United States Agency for International Development (USAID), and the World Health Organization (WHO) as a treatment for diarrhea. Although the product is not approved by the FDA, USP is giving this monograph special consideration to support efforts by the aforementioned organizations to ensure the availability of quality public standards for the product marketed outside the United States.

(DSN: L. Evans; PSD: C. Okeke; NL: C. Barnstein; BPC: M. Marques) RTS—41759-1; 41759-2

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Add the following:

▲Zinc Sulfate Tablets

» Zinc Sulfate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $ZnSO_4 \cdot H_2O$. It may contain one or more suitable flavors and sweeteners.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Labeling—Label the Tablets in terms of zinc sulfate ($ZnSO_4 \cdot H_2O$) and in terms of elemental zinc.

Identification—

*Test solution—*Dissolve the equivalent of 1 g of finely powdered Tablets in 50 mL of water. Use in the following two tests.

A: To 5 mL of the *Test solution* add 0.2 mL of concentrated sodium hydroxide. A white precipitate is formed. Dissolve the precipitate in 2 mL of concentrated sodium hydroxide. The solution remains clear after the addition of 10 mL of ammonium chloride solution and forms a white precipitate after the addition of 0.1 mL of sodium sulfide solution.

B: To 5 mL of the *Test solution* add 1 mL of dilute hydrochloric acid and 1 mL of barium chloride TS. A white precipitate is formed.

Dissolution—

Medium: purified water with resistivity below 1 µS/cm; 750 mL.

Apparatus: basket-rack assembly (see *Disintegration* ⟨701⟩).

Time: 20 seconds.

*Procedure—*Place 1 Tablet in each of the six tubes of the basket, lower the basket-rack assembly into the beaker containing the *Medium,* and introduce the electrode of the resistivity meter into the beaker without hindering the motion of the basket. Measure the resistivity every 2 seconds.

*Tolerances—*The disintegration of the Tablets is complete in 20 seconds, and the resistivity stabilizes at about 255 to 260 µS in 20 seconds.

Uniformity of dosage units ⟨905⟩**—**meet the requirements.

Assay—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 90 mg of zinc, to a 200-mL volumetric flask. Dissolve in 15 mL of dilute acetic acid, and sonicate for 15 minutes. Dilute with water to volume, and mix. Add 50 mg of xylenol orange triturate to the solution, and mix. Neutralize the solution with about 2 g of methenamine until the solution is a violet-pink color. Titrate with 0.1 M edetate disodium VS until the solution is yellow. Each mL of 0.1 M edetate disodium VS is equivalent to 17.946 mg of $ZnSO_4 \cdot H_2O$.▲*USP29*

In-Process Revision

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Choline Chloride, *USP 28* page 2067 and page 951 of *PF* 30(3) [May–June 2004]. It is proposed to revise the *Procedure* in the test for *Limit of total amines* to correct the equation used to calculate the correction factor (*F*).

(DSN: L. Evans) RTS—41895-1

Change to read:

Limit of total amines—

Standard solution—Dissolve an accurately weighed quantity of trimethylamine hydrochloride in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of 500 µg per mL.

Test solution—Transfer 10.0 g of Choline Chloride to a beaker containing a plastic-coated stirring bar, add 170 mL of water and 30.0 mL of sodium hydroxide TS, and stir until dissolved.

System suitability solution—Dissolve an accurately weighed quantity of trimethylamine hydrochloride in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution containing 10 µg of trimethylamine hydrochloride per mL. Transfer 10.0 mL of this solution to a beaker containing a plastic-coated stirring bar, add 170 mL of water and 30.0 mL of sodium hydroxide TS, and stir until dissolved.

Electrode system—Use a gas-sensing, ammonia-specific indicating electrode with internal reference connected to a pH meter capable of measuring potentials with a minimum reproducibility of ± 0.1 mV (see *pH* ⟨791⟩).

Standard response line—Transfer 30.0 mL of sodium hydroxide TS to a suitable beaker, and add enough water to give a total volume of 200 mL. Add a plastic-coated stirring bar, insert the electrode into the solution, and record the potential, in mV. Continue stirring, and at 5-minute intervals add 0.200, 0.600, 1.00, and 2.00 mL of *Standard solution*, and record the potential after each addition. Plot the logarithms of the cumulative trimethylamine concentrations (0.50, 1.50, 2.50, and 5.00 µg per mL) versus potential, in mV, and determine the slope *(S)* of the *Standard response line* for the electrode.

System suitability—Proceed with the *System suitability solution* as directed for *Test solution* for *Procedure* and measure the potentials: the trimethylamine equivalent is between 8.5 and 11.5 mg per liter.

Procedure—Rinse the electrode, insert it into the *Test solution,* stir, and record the potential, in mV. Add 0.100 mL of the *Standard solution,* and record the potential. Add another 0.100 mL of the *Standard solution,* and record the potential. [NOTE—If the total change after the second addition of the *Standard solution* is less than 10 mV, add a third aliquot of 0.200 mL.] Calculate the quantity, in µg per g, of total amines in the portion of Choline Chloride taken by the formula:

$$500V_A/(F-1)W,$$

in which V_A is the total volume of the *Standard solution* added to the *Test solution; W* is the weight, in g, of Choline Chloride taken to prepare the *Test solution;* and the correction factor, *F,* is calculated by the formula:

~~antilog $(mV_0 - mV_F)/S$,~~

~~in which *mVo* is the initial reading, in mV, of the *Test solution; mV~F~* is the final reading, in mV, after the additions of the *Standard solution;*~~

▲antilog $[(mV_F - mV_0)/S]$,

in which mV_F is the final reading, in mV, after the additions of the *Standard solution*; mV_0 is the initial reading, in mV, of the *Test solution;* ▲*USP29*
and *S* is the slope of the *Standard response line* for the electrode: not more than 0.001% is found.

Change to read:

Chromatographic purity—

Buffer solution—Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile ~~(50 : 50).~~

■(70 : 30).■1S *(USP28)*

Standard solution—Transfer an accurately weighed amount, not more than 100 mg, of USP Choline Chloride RS to a 24-mL screw-capped vial, and add 400 mg of 3,5-dinitrobenzoyl chloride and 10 mL of acetonitrile. Cap the vial, heat to 55°, and continue heating for ~~1 hour.~~

■2 hours.■1S *(USP28)*
Cool to room temperature, and add 5 mL of water. Allow to stand for ~~2 minutes.~~

■5 minutes.■1S *(USP28)*
Quantitatively transfer the solution to a 25-mL volumetric flask, dilute with acetonitrile to volume, and mix. Dilute a volume of this solution with *Mobile phase* to obtain a solution having a known concentration of 2.0 µg of USP Choline Chloride RS per mL.

Test solution—Transfer about 110 mg of Choline Chloride, accurately weighed, to a 24-mL screw-capped vial. Dry at 120° for 2 hours. Add 400 mg of 3,5-dinitrobenzoyl chloride and 10 mL of acetonitrile. Cap the vial, heat to 55°, and continue heating for ~~1 hour.~~

■2 hours.■1S *(USP28)*
Cool to room temperature, and add 5 mL of water. Allow to stand for ~~2 minutes.~~

■5 minutes.■1S *(USP28)*
Quantitatively transfer the solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

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■Pipet 2.0 mL of the solution into a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.■1S *(USP28)*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 208-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The column temperature is maintained at 30°. 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; and the relative standard deviation determined from the choline chloride derivative peak 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 all the peak responses. Calculate the percentage of each impurity in the portion of Choline Chloride taken by the formula:

~~$5000(C/W)(r_i/r_s),$~~

■$62{,}500(C/W)(r_i/r_S),$■1S *(USP28)*

in which C is the concentration, in mg per mL, of USP Choline Chloride RS in the *Standard solution;* W is the weight, in mg, of Choline Chloride taken to prepare the *Test solution;* r_i is the peak response for each impurity, other than that for the choline chloride derivative and 3,5-dinitrobenzoic acid obtained from the *Test solution;* and r_S is the peak response for the choline chloride derivative obtained from the *Standard solution:* not more than 0.3% of any individual impurity is found; and not more than 2.0% of total impurities is found.

BRIEFING

Chondroitin Sulfate Sodium Tablets, *USP 28* page 2069 and page 2071 of *PF* 30(6) [Nov.–Dec. 2004]; **Glucosamine and Chondroitin Sulfate Sodium Tablets,** *USP 28* page 2102 and page 2072 of *PF* 30(6) [Nov.–Dec. 2004]. The current label requires declaration of the species used to prepare the chondroitin sulfate sodium. The monograph allows preparation from bovine, avian, and porcine cartilages. A request to remove the species declaration, based on the lack of validated tests to determine the origin, was received at USP. After consideration of the request, the committee decided to retain the declaration of the sources in the labeling section of the monograph with minor clarifying language. The current official monograph for Chondroitin Sulfate Sodium Tablets directs that the label state the content of chondroitin sulfate sodium on the dried basis, but also allows the label to state the content on the hydrous basis. Because prominence could be given to either the dried weight or the hydrous weight, leading to consumer confusion, it is proposed to modify the labeling statement by requiring declaration of the dried content on the front panel of the labels. In the absence of any adverse comment, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of June 1, 2005.

(DSB: G. Giancaspro) RTS—41084-1

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.~~

•Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis.•3

BRIEFING

Glucosamine and Chondroitin Sulfate Sodium Tablets, *USP 28* page 2102 and page 2072 of *PF* 30(6) [Nov.–Dec. 2004]—See briefing under *Chondroitin Sulfate Sodium Tablets.* In the absence of any adverse comment, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of June 1, 2005.

(DSB: G. Giancaspro) RTS—41084-2

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.~~

•Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis.•3

BRIEFING

Ubidecarenone, *USP 28* page 2132. It is proposed to introduce a new USP Reference Standard, USP Ubidecarenone Related Compound A RS, for coenzyme Q_9.

(DSN: L. Evans) RTS—42048-1

Change to read:

USP Reference standards ⟨11⟩—*USP Ubidecarenone RS.*

▲*USP Ubidecarenone Related Compound A RS.*▲*USP29*
USP Ubidecarenone for System Suitability RS.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol and dehydrated alcohol (13 : 7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve accurately weighed quantities of USP Ubidecarenone RS and ~~coenzyme Q_9~~ ▲USP Ubidecarenone Related Compound A RS▲*USP29* in dehydrated alcohol, heating at about 50° for 2 minutes if necessary, to obtain a solution having known concentrations of about 0.5 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ubidecarenone RS in dehydrated alcohol, heating at about 50° for 2 minutes if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Transfer about 50 mg of Ubidecarenone, accurately weighed, to a 50-mL volumetric flask, dissolve in dehydrated alcohol, heating at about 50° for 2 minutes if necessary, cool, dilute with dehydrated alcohol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 5-mm × 15-cm column that contains packing L1, and is maintained at a temperature of 35°. The flow rate is adjusted to obtain a retention time of about 11 minutes. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for ~~coenzyme Q_9~~ ▲ubidecarenone related compound A▲*USP29* and 1.0 for ubidecarenone; the resolution, *R,* between ~~coenzyme Q_9~~ ▲ubidecarenone related compound A▲*USP29* and ubidecarenone is not less than 4; and the relative standard deviation for replicate injections is not more than 0.8%.

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 responses for the major peaks. Calculate the quantity, in mg, of $C_{59}H_{90}O_4$ in the portion of Ubidecarenone taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Ubidecarenone 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

Ubidecarenone Capsules, *USP 28* page 2132. It is proposed to introduce a new USP Reference Standard, USP Ubidecarenone Related Compound A, for coenzyme Q_9.

(DSN: L. Evans) RTS—42048-2

Change to read:

USP Reference standards ⟨11⟩—*USP Ubidecarenone RS.*

▲*USP Ubidecarenone Related Compound A RS.*▲*USP29*

Change to read:

Assay—[NOTE—Conduct this test promptly with minimum exposure to actinic light.]

Solvent—Prepare a mixture of *n*-hexane and dehydrated alcohol (5 : 2).

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and water (55 : 40 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ubidecarenone RS in *Solvent* to obtain a solution having a known concentration of 1.0 mg per mL. Dilute a portion of this solution with dehydrated alcohol to obtain a solution having a known concentration of about 40 µg per mL.

Resolution solution—Dissolve an accurately weighed quantity of ~~coenzyme Q_9~~ ▲USP Ubidecarenone Related Compound A RS▲*USP29* in *Solvent* to obtain a solution having a concentration of 1.0 mg per mL. Dilute a portion of this solution with dehydrated alcohol to obtain a solution having a concentration of about 40 µg per mL. Mix equal volumes of this solution and the *Standard preparation.*

Assay preparation 1 (for soft gelatin Capsules)—Using a suitable cutting instrument, open an accurately counted number of Capsules, equivalent to about 200 mg of ubidecarenone. Quantitatively transfer the shells and contents to a suitable container, add 100 mL of *Solvent,* and shake by mechanical means for 30 minutes. Using small portions of *Solvent,* quantitatively transfer this mixture to a 200-mL volumetric flask, dilute with *Solvent* to volume, and mix. Centrifuge a portion of this solution, transfer 1.0 mL of the supernatant to a 25-mL volumetric flask, add 2.5 mL of a 0.1% solution of anhydrous ferric chloride in alcohol, ▲dilute with alcohol to volume,▲*USP28* and mix.

Assay preparation 2 (for hard gelatin Capsules)—Empty and thoroughly mix the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of ubidecarenone, to a 100-mL volumetric flask, add 60 mL of *Solvent,* and shake by mechanical means for 30 minutes. Dilute with *Solvent* to volume, and mix. Centrifuge a portion of this solution, transfer 1.0 mL of the supernatant to a 25-mL volumetric flask, add 2.5 mL of a 0.1% solution of anhydrous ferric chloride in alcohol, dilute with alcohol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and an 8-mm × 10-cm column that contains packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ubidecarenone and ~~coenzyme Q_9~~

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▲ubidecarenone related compound A▲*USP29*
is not less than 2.5. 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 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and *Assay preparation 1* or *Assay preparation 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ubidecarenone ($C_{59}H_{90}O_4$) in each soft gelatin Capsule taken by the formula:

$$5000(C/N)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Ubidecarenone RS in the *Standard preparation; N* is the number of Capsules taken to prepare *Assay preparation 1;* and r_U and r_S are the peak responses obtained from *Assay preparation 1* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of ubidecarenone ($C_{59}H_{90}O_4$) in the portion of hard gelatin Capsules taken by the formula:

$$2500C(r_U / r_S),$$

in which r_U is the peak response obtained from *Assay preparation 2;* and the other terms are as defined herein.

MONOGRAPHS (NF)

BRIEFING

Acesulfame Potassium, *NF 23* page 2947 and page 591 of *PF* 30(2) [Mar.–Apr. 2004]; **Adipic Acid,** *NF 23* page 2950 and page 1322 of *PF* 30(4) [July–Aug. 2004]; **Galactose,** *NF 23* page 3008 and page 600 of *PF* 30(2) [Mar.–Apr. 2004]; **Sodium Tartrate,** *NF 23* page 3082 and page 611 of *PF* 30(2) [Mar.–Apr. 2004]; **Succinic Acid,** *NF 23* page 3093 and page 612 of *PF* 30(2) [Mar.–Apr. 2004]. It is proposed to add a *Packaging and storage* statement in accordance with the current policies of the Packaging, Storage and Distribution Expert Committee.

(EMC: K. Russo; PSD: C. Okeke) RTS—41917-1

Add the following:

▲**Packaging and storage**—Preserve in a well-closed container, and protect from light. Store at room temperature.▲*NF24*

BRIEFING

Adipic Acid, *NF 23* page 2950 and page 1322 of *PF* 30(4) [July–Aug. 2004]—See briefing under *Acesulfame Potassium*.

(EMC: K. Russo; PSD: C. Okeke) RTS—41917-2

Add the following:

▲**Packaging and storage—**Preserve in a tight container. No storage requirements specified.▲*NF24*

Add the following:

■**USP Reference standards** ⟨**11**⟩—*USP Adipic Acid RS.*■1S (*NF23*)

BRIEFING

Asparagine, *NF 23* page 2959 and page 205 of *PF* 30(1) [Jan.–Feb. 2004]. Because this monograph covers both anhydrous and monohydrate forms of Asparagine, it is proposed to introduce two USP Reference Standards—one for the anhydrous form and one for the monohydrate form. It is also proposed to add a note under the *Identification* and *Chromatographic purity* tests to clarify that each form of Asparagine should be evaluated using the appropriate Reference Standard.

(EMC: E. Gonikberg) RTS—42000-1

Add the following:

▲**Packaging and storage**—Preserve in well-closed, light-resistant containers. ~~Store at room temperature, and avoid excessive heat and freezing. Protect from moisture.~~ Store at room temperature.▲*NF24*

Change to read:

USP Reference standards ⟨11⟩~~— *USP Asparagine RS.*~~

▲*USP Asparagine Anhydrous RS. USP Asparagine Monohydrate RS.*▲*NF24*

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Change to read:

Identification, *Infrared Absorption* ⟨197K⟩.

▲[NOTE—Use USP Asparagine Anhydrous RS and USP Asparagine Monohydrate RS for the evaluation of the anhydrous and monohydrate forms of Asparagine, respectively.]▲*NF24*

Change to read:

Chromatographic purity—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution: 10 mg per mL.

Standard solution—Prepare a solution of ~~USP Asparagine RS~~ ▲USP Asparagine Anhydrous RS or USP Asparagine Monohydrate RS▲*NF24* in water having a known concentration of about 0.05 mg per mL.

▲[NOTE—Use USP Asparagine Anhydrous RS and USP Asparagine Monohydrate RS for the evaluation of the anhydrous and monohydrate forms of Asparagine, respectively.]▲*NF24*

Application volume: 5 µL.

Developing solvent system: a mixture of butyl alcohol, water, and glacial acetic acid (3 : 1 : 1).

Spray reagent—Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and glacial acetic acid (95 : 5).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩, and then dry the plate at 80° for 30 minutes. Spray the plate with the *Spray reagent,* heat at 80° for 10 minutes, and examine under white light: no secondary spot in the chromatogram obtained from the *Test solution* is larger or more intense than the principal spot in the chromatogram obtained from the *Standard solution* (0.5%); and not more than 1.0% of total impurities is found.

BRIEFING

Ferric Oxide, *NF 23* page 3006. On the basis of comments received, it is proposed to revise the limit indicated in the test for *Acid-insoluble substances* to reflect the material currently available for pharmaceutical applications. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of June 1, 2005.

(EMC: C. Sheehan) RTS—41462-1; 41462-2

Change to read:

Acid-insoluble substances—Digest 2.0 g in 25 mL of hydrochloric acid by boiling for 20 minutes. Add 100 mL of hot water, and filter quantitatively through a tared filtering crucible with the aid of hot wash water until the filtrate tests negative for chloride. Dry the crucible and contents at 105° for 1 hour: the residue weighs not more than ~~2 mg (0.1%).~~ •6 mg (0.3%).•3

BRIEFING

Galactose, *NF 23* page 3008 and page 600 of *PF* 30(2) [Mar.–Apr. 2004]—See briefing under *Acesulfame Potassium*.

(EMC: K. Russo; PSD: C. Okeke) RTS—41917-3

Add the following:

▲**Packaging and storage**—Preserve in a tight container. No storage requirements specified.▲*NF24*

BRIEFING

Isomalt. Because there is no existing *NF* monograph for this article, the following new monograph, based on submitted data, is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the BioRad HPX-87 C brand of L19 column. The typical retention time for 1-*O*-α-D-Glucopyranosyl-D-mannitol (1,1-GPM) in the *Related compounds* test is about 12.3 minutes.

(EMC: D. Bempong; PSD: C. Okeke; NL: C. Barnstein) RTS—40631-1

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Add the following:

▲Isomalt

$C_{12}H_{24}O_{11}$ 344.32

6-*O*-α–Glucopyranosyl-D-sorbitol.

6-*O*-α-D-Glucopyranosyl-D-glucitol.

$C_{12}H_{24}O_{11} \cdot 2H_2O$ 380.32

1-*O*-α-D-Glucopyranosyl-D-mannitol dihydrate [*64519-82-0*].

» Isomalt contains not less than 98.0 percent and not more than 102.0 percent of a mixture of 6-*O*-α-D-glucopyranosyl-D-sorbitol (1,6-GPS) and 1-*O*-α-D-glucopyranosyl-D-mannitol (1,1-GPM), and neither of the two components is less than 3.0 percent of the mixture, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

Labeling—Label it to indicate the percentage content of 1,6-GPS and 1,1-GPM.

USP Reference standards ⟨11⟩—*USP Isomalt RS. USP Mannitol RS. USP Sorbitol RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture containing a fluorescent indicator having optimal intensity at 254 nm.

Test solution: 5000 µg per mL in water.

Application volume: 1 µL.

Developing solvent system: a mixture of ethyl acetate, pyridine, water, acetic acid, and propionic acid (50 : 50 : 10 : 5 : 5).

Procedure—Separately apply 1 µL each of the Standard solution and the *Test solution* to the thin-layer chromatographic plate, and thoroughly dry the starting points in warm air. Develop over 10 cm using the *Developing solvent system*, dry the plate in a current of hot air, and dip for 3 seconds in a 1 g per L solution of sodium periodate. Dip the plate for 3 seconds in a mixture of dehydrated alcohol, sulfuric acid, acetic acid, and anisaldehyde (90 : 5 : 1 : 1). Dry the plate in a current of hot air until colored spots become visible. The background color may be brightened by exposure to warm steam. Examine in daylight. The chromatogram obtained from the Standard solution shows two blue-grey spots with R_F values of about 0.13 (1,6-GPS) and 0.16 (1,1-GPM). The chromatogram obtained from the *Test solution* shows principal spots similar in position and color to the chromatogram obtained from the Standard solution.

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

Conductivity—Dissolve 20 g in carbon dioxide-free water prepared from distilled water, and dilute with the same solvent to 100 mL. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard, measure the conductivity of the solution while gently stirring with a magnetic stirrer. The conductivity of the test solution is not more than 20 µS per cm.

Water, *Method I* ⟨921⟩**:** not more than 7% determined on 0.3 g. Use a mixture of anhydrous methanol and formamide (1 : 1) as solvent at 50 ± 5°.

Heavy metals, *Method I* ⟨231⟩**:** 10 µg per g.

Reducing sugars—Dissolve 3.3 g in 10 mL of Purified Water with the aid of gentle heat. Cool, and add 20 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 dilute acetic acid, 60 mL of water, and 20 mL of 0.025 M 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 iodine with 0.05 N sodium thiosulfate VS using 1 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, determined on the anhydrous basis, as glucose.

Limit of nickel—[NOTE—The purity of the reagents and the water used must be suitable for trace analysis, and the reagents and water must be free of nickel.]

Nickel standard solution—Transfer 1 mL of nickel standard solution TS into a 100-mL volumetric flask, add 1 mL of nitric acid, dilute with water to volume, and mix. This solution contains the equivalent of 0.1 µg of nickel per mL.

Test solution—Accurately weigh about 8 g of Isomalt into a 50-mL volumetric flask, add 8 mL of water and 3 mL of 65% nitric acid solution, and incubate at 95° for 1 hour. Allow the solution to cool to room temperature, add another 3 mL of 65% nitric acid solution, and incubate at 95° until all brown vapors have dissipated (about 1–1.5 hours). Allow the solution to cool to room temperature, carefully add 3 mL of 30 percent hydrogen peroxide, and keep the solution at 95° until the evolution of gas has ceased (about 1–2 hours). Allow the solution to cool to room temperature. Repeat the procedure two more times, i.e., adding 30 percent hydrogen peroxide, heating to 95°, and cooling to room temperature. Dilute the resulting solution with water to 50 mL.

Blank—Prepare as directed for the *Test solution,* except to omit the addition of Isomalt.

Standard solutions—Into seven identical 10-mL volumetric flasks, introduce respectively 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mL of *Nickel standard solution* equivalent to 0, 0.05, 0.1, 0.15, 0.2, 0.25, and 0.3 µg of nickel. To each flask, add a 2.0-mL portion of the *Test solution,* and dilute with water to volume.

Blank solutions—Prepare as directed for *Standard solutions* except to replace 2 mL of the *Test solution* with 2 mL of the *Blank*.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Blank solutions* 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 graphite furnace and a nickel hollow-cathode lamp. Record the average of the steady readings for each of the *Standard solutions* and the *Blank solutions*. Plot the absorbances of the *Standard solutions* versus the quantity of nickel, in µg, in the portion of *Nickel standard solution* added to each *Standard solution* flask. 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 amount of nickel (A_T), in µg, present in the portion of *Test solution* that was added to each of the *Standard solution* flasks. Similarly, plot the absorbance of the *Blank solutions* versus the quantity of nickel, in µg, in the portion of *Nickel standard solution* added to each of the *Blank solution* flasks, to determine the quantity of nickel (A_B) in the portion of

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Blank added to each of the *Blank solution* flasks. Calculate the quantity, in µg, of nickel in the portion of Isomalt taken by the formula:

$$25(A_T - A_B).$$

Not more than 1 µg per g, calculated on the anhydrous basis, is found.

Related compounds—

Mobile phase—Prepare as directed in the *Assay.*

Resolution solution—Dissolve accurately weighed quantities of USP Isomalt RS, USP Mannitol RS, and USP Sorbitol RS, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 20 mg per mL, 0.1 mg per mL, and 0.1 mg per mL, respectively.

Standard solution—Dissolve an accurately weighed quantity of USP Sorbitol RS and USP Mannitol 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 of each per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the typical retention time of 1,1-GPM is about 12.3 minutes; the relative retention times are about 1.2 for 1,6-GPS, about 1.6 for mannitol, about 2.0 for sorbitol, and 1.0 for 1,1-GPM; and the resolution, *R,* between 1,1-GPM and 1,6-GPS is not less 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 mannitol or sorbitol in the portion of Isomalt taken by the formula:

$$5000C/W(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Mannitol RS or USP Sorbitol RS in the *Standard solution;* and r_U and r_S are the individual peak responses of mannitol or sorbitol obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.5% of mannitol and not more than 0.5% of sorbitol is found. Calculate the percentage of any other impurity in the portion of Isomalt 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 obtained from the *Test solution:* not more than 0.5% of any individual impurity is found; and not more than 2.0% of total impurities, including mannitol and sorbitol, is found. Disregard any impurity peak that is less than 0.1%.

Assay—

Mobile phase—Use degassed water.

Standard preparation—Dissolve an accurately weighed quantity of USP Isomalt RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 20 mg per mL.

Assay preparation—Transfer about 1000 mg of Isomalt, 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 refractive index detector maintained at a constant temperature, a 7.8-mm × 30-cm column that contains packing L19, and a 4.6-mm × 3-cm guard column that contains packing L19. The flow rate is about 0.5 mL per minute. The column temperature is maintained at 80 ± 1°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for 1,6-GPS and 1.0 for 1,1-GPM; the resolution, *R,* between 1,1-GPM and 1,6-GPS is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%, determined from the 1,6-GPS and 1,1-GPM peak responses.

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 1,6-GPS and 1,1-GPM peaks. Calculate the quantity, in mg, of 1,6-GPS in the portion of Isomalt taken by the formula:

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

in which C is the concentration, in mg per mL, of 1,6-GPS in the *Standard preparation,* with calculation based on the declared 1,6-GPS content of USP Isomalt RS; and r_U and r_S are the 1,6-GPS peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. Similarly, calculate the quantity, in mg, of 1,1-GPM in the portion of Isomalt taken.▲*NF24*

BRIEFING

Lauroyl Macrogolglycerides, page 1212 of *PF* 28(4) [July–Aug. 2002]. It is proposed to adopt Lauroyl Polyoxylglycerides as the title of this proposed new monograph. A monograph for this excipient first appeared in *Pharmacopeial Previews* in *PF* 24(5) [Sept.–Oct. 1998] and under *In-Process Revision* in *PF* 28(4) [July–Aug. 2002] with the name Lauroyl Macrogolglycerides. The name Lauroyl Polyoxylglycerides is proposed by the Expert Committee on Nomenclature and Labeling to be the title of the monograph for this excipient, which is proposed for inclusion in *NF 24,* but with an official date of January 1, 2011, which is 60 months later than January 1, 2006, the official date of *NF 24.* The 60-month extension will provide the time deemed necessary for labeling changes to be made for the article and the numerous preparations in which it is an ingredient, and for practitioners, consumers, and regulatory agencies to become familiar with the terminology.

Use of the prefix "polyoxyl-" instead of "macrogol-" is consistent with the terminology used in the United States, particularly in the titles of other monographs on excipients. The "polyethylene glycol" and "polyoxyl-" designation for esters and ethers formed with polyethylene glycol and organic acid and alcohols or polyols replaces the "macrogol" designation that is used for polyethylene glycol in some locations outside the United States.

(EMC: C. Sheehan; NL: C. Barnstein) RTS—41993-1

Add the following:

▲Lauroyl ~~Macrogolglycerides~~ Polyoxylglycerides

(Title for this new monograph—to become official January 1, 2011)

(Prior to January 1, 2011, it is expected that the current practice of labeling the article of commerce with the name Lauroyl Macrogolglycerides will be continued.)

» Lauroyl ~~Macrogolglycerides~~ Polyoxylglycerides are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of ~~macrogols~~ polyethylene glycols with a mean relative molecular weight between 300 and 1500. They are produced by partial alcoholysis of saturated oils, mainly containing triglycerides of lauric acid with ~~macrogol~~ polyethylene glycols, by esterification of glycerol and ~~macrogol~~ polyethylene glycols with fatty acids, or as a mixture

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of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. 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 nominal saponification value.

USP Reference standards ⟨11⟩—*USP Lauroyl ~~Macrogolglycerides~~ 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⟩**:** between 36 and 85, 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⟩**:** between 79 and 204, determined on a 2.0-g specimen.

Fatty acid composition ⟨401⟩**:** not more than 15.0% of caprylic acid is found; not more than 12.0% of capric acid is found; between 30% and 50% of lauric acid is found; between 5% and 25% of myristic acid is found; between 4% and 25% of palmitic acid is found; and between 5% and 35% 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 0.1%, 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.▲*NF24*

BRIEFING

Methacrylic Acid Copolymer, *NF 23* page 3035. On the basis of comments received, it is proposed to revise the *Phosphate buffer* in the test for *Limit of monomers* to change the term ''fortieth-molar'' to ''0.025 M'' and to indicate the use of the anhydrous form of dibasic sodium phosphate to be consistent with the *Reagent Specifications* section of *USP 28–NF 23.*

(EMC: C. Sheehan) RTS—42046-1

Change to read:

Limit of monomers—
~~*pH 2.0 Phosphate buffer, fortieth molar*~~

▲*pH 2.0 Phosphate buffer, 0.025 M*▲*NF24*
—Prepare an aqueous solution containing 3.550 g of

▲anhydrous▲*NF24*
dibasic sodium phosphate (Na_2HPO_4) and 3.400 g of monobasic potassium phosphate (KH_2PO_4) per L. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase—Prepare a solution in methanol to contain 700 mL of ~~*pH 2.0 Phosphate buffer, fortieth molar*~~

▲*pH 2.0 Phosphate buffer, 0.025 M*▲*NF24*
per L.

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Standard solution—Prepare a solution in methanol to contain an accurately known concentration of about 2.4 µg per mL each of methacrylic acid and either methyl methacrylate (for Type A and Type B) or ethyl acrylate (for Type C). To 50.0 mL of this solution, add 25.0 mL of water, and mix.

Test solution—Dissolve about 40 mg of Methacrylic Acid Copolymer, accurately weighed, in 50.0 mL of methanol, add 25.0 mL of water, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 202-nm detector and a 4-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* of each pair of analytes is not less than 2.0; the capacity factors, k', for methacrylic acid, ethyl acrylate, and methyl methacrylate are 1.7, 4.3, and 4.8, respectively; and the relative standard deviation for replicate injections determined from each analyte 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 quantity, in µg, of each monomer in the portion of Methacrylic Acid Copolymer taken by the formula:

$$75C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of the monomer in the *Standard solution;* and r_U and r_S are the peak responses for the monomer obtained from the *Test solution* and the *Standard solution*, respectively. Not more than 0.05% of total monomers is found.

BRIEFING

Phenolsulfonphthalein, *USP* 28 page 3048 and page 988 of *PF* 30(3) [May–June 2004]. Comments were received that specific limits for the test for *Bacterial endotoxins* should not be included in the excipient monograph because the excipient could be used in multiple finished products with differing limits for bacterial endotoxins. On the basis of these comments, it is proposed to revise the requirements in the test for *Bacterial endotoxins*.

(EMC: E. Gonikberg; AMB: R. Tirumalai) RTS—42043-1

Add the following:

■**Packaging and storage**—Preserve in well-closed containers. ~~Store at 25°, excursions permitted between 15° and 30°.~~ No storage requirements specified.■1S *(NF23)*

Add the following:

▲**Labeling**—Where it is intended for use in articles administered parenterally, it is so labeled.▲*NF24*

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*▲*NF24*

Add the following:

▲**Bacterial endotoxins** ⟨85⟩—Where it is intended for use in articles administered parenterally, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Phenolsulfonphthalein is used can be met.▲*NF24*

BRIEFING

Phenoxyethanol, *NF* 23 page 3048 and page 208 of *PF* 30(1) [Jan.–Feb. 2004]. Because *Phenoxyethanol* could be used in articles administered parenterally, it is proposed to add the test for *Bacterial endotoxins* and an appropriate *Labeling* requirement. See also briefing under *Phenolsulfonphthalein*.

(EMC: E. Gonikberg; AMB: R. Tirumalai) RTS—42043-2

Add the following:

▲**Labeling—**Where it is intended for use in articles administered parenterally, it is so labeled.▲*NF24*

Change to read:

USP Reference standards ⟨11⟩**—**

▲*USP Endotoxin RS.*▲*NF24*
USP Phenoxyethanol RS.

Add the following:

▲**Bacterial endotoxins** ⟨85⟩—Where it is intended for use in articles administered parenterally, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Phenoxyethanol is used can be met.▲*NF24*

In-Process Revision

BRIEFING

Polyethylene Oxide, *NF 23* page 3057. In the test for *Organic volatile impurities,* it is proposed to delete the instructions for preparation of the *Standard solution* and the *Test solution* because the USP general chapter *Organic Volatile Impurities* ⟨467⟩ has since been revised and these instructions are no longer necessary.

(EMC: K. Russo) RTS—41787-3

Change to read:

Organic volatile impurities, *Method I* ⟨467⟩**:** meets the requirements.

~~*Standard solution* and *Test preparation*—Prepare a *Test preparation* having a concentration of 20 mg per mL, and prepare a *Standard solution* having twice the stated concentration.~~

▲▲*NF24*

BRIEFING

Sodium Tartrate, *NF 23* page 3082 and page 611 of *PF* 30(2) [Mar.–Apr. 2004]—See briefing under *Acesulfame Potassium*.

(EMC: K. Russo; PSD: C. Okeke) RTS—41917-4

Add the following:

▲**Packaging and storage**—Preserve in a tight container. No storage requirements specified.▲*NF24*

BRIEFING

Succinic Acid, *NF 23* page 3093 and page 612 of *PF* 30(2) [Mar.–Apr. 2004]—See briefing under *Acesulfame Potassium*.

(EMC: K. Russo; PSD: C. Okeke) RTS—41917-5

Add the following:

▲**Packaging and storage**—Preserve in a well-closed container. No storage requirements specified.▲*NF24*

BRIEFING

Sunflower Oil, page 2803 of *PF* 27(4) [July–Aug. 2001]. Following the comments received for the preview published on page 1422 of *PF* 26(5) [Sept.–Oct. 2000], this revision is proposed. The gas chromatographic procedure that appeared in the preview article has been modified to improve the chromatography. The procedure modification is along the lines of general test chapter *Fats and Fixed Oils* ⟨401⟩. Interested parties are encouraged to try the procedure and submit comments to USP Headquarters for consideration. In addition, minor editorial style changes have been made.

(EMC: R. Ravichandran; PSD: C. Okeke) RTS—41367-1

Add the following:

▲Sunflower Oil

» Sunflower Oil is a refined fixed oil obtained from the seeds of the sunflower plant *Helianthus annuus* Linné (Fam. Asteraceae alt. Compositae).

Packaging and storage—Preserve in tight, light-resistant containers. ~~, and avoid exposure to excessive heat.~~ No storage requirement specified.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant source from which the article was derived. The label also indicates the name and concentration of any additive.

Specific gravity ⟨841⟩**:** between 0.914 and 0.924 at 20°.

Free fatty acids ⟨401⟩**:** not more than 2.5 mL of 0.020 N sodium hydroxide is required for neutralization.

Iodine value, *Method II* ⟨401⟩**:** between 128 and 148 for generic Oil, between 98 and 118 for mid-oleic Oil, and between 78 and 98 for high-oleic Oil.

Saponification value ⟨401⟩**:** between 180 and 200.

Unsaponifiable matter ⟨401⟩**:** not more than 1.0%.

Fatty acid composition—

~~*0.1 N Methanolic potassium hydroxide solution*—Dissolve 34 g of potassium hydroxide in a sufficient volume of methanol to obtain a final volume of 500 mL, allow to stand for 24 hours in a tightly stoppered bottle, and decant the clear supernatant.~~

Standard solution—Prepare an ester mixture containing methyl palmitate, methyl stearate, methyl oleate, methyl linoleate, and methyl linolenate (7 : 5 : 35 : 50 : 3). [NOTE—Ester mixtures are available commercially from Nu-Chek-Prep, Inc., P.O. Box 295, Elysian, MN 56028. Typical Nu-Chek-Prep ester mixtures useful in this test include Nu-Chek 15A.This mixture may contain other components.]

Test solution—~~Place about 1 g of Oil in a small conical flask fitted with a reflux condenser. Add 10 mL of methanol and 0.5 mL of *0.1 N Methanolic potassium hydroxide solution*. Reflux the mixture for 10 minutes, cool, transfer to a separator with the aid of 15 mL of *n* heptane, add 10 mL of saturated sodium chloride solution, shake, and allow to separate. Transfer the lower layer to another separator, add 10 mL of *n* heptane, and shake. Wash the combined organic layers with 10 mL of water, dry over anhydrous sodium sulfate, and filter.~~ Transfer about 100 mg of the test specimen to a 50-mL conical flask fitted with a suitable water-cooled reflux condenser and a magnetic stir bar. Add 4 mL of 0.5 N methanolic sodium hydroxide solution, and reflux until fat globules disappear (usually 5 to 10 minutes). Add 5 mL of a solution prepared by dissolving 14 g of boron trifluoride in methanol to make 100 mL, swirl to mix, and reflux for 2 minutes. Add 4 mL of chromatographic *n*-heptane through the condenser, and reflux for 1 minute. Cool, remove the condenser, add about 15 mL of saturated sodium chloride solution, shake, and allow the layers to separate. Pass the *n*-heptane layer through 0.1 g of anhydrous sodium sulfate (previously washed with chromatographic *n*-heptane) into a suitable flask. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with chromatographic *n*-heptane to volume, and mix.

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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 capillary column bonded with a 0.25-µm layer of phase G5. The carrier gas is hydrogen, flowing at a rate of 1 mL per minute. The injection port and detector temperatures are maintained at 250°, and the column temperature is maintained at 175°.~~ The gas chromatograph is equipped with a flame-ionization detector maintained at a temperature of about 250°, a splitless injection system, and a 0.25-mm × 30-m fused-silica capillary column bonded with a 0.25-µm layer of phase G5. The column temperature is maintained at 120° for about 2 minutes after injection, and the temperature is then increased at the rate of 4° per minute to 240° and maintained at 240° for 5 minutes. The injection port temperature is maintained at about 220°. The carrier gas is hydrogen, with a flow rate of about 1 mL per minute. Chromatograph 1 µL of the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.87 for methyl palmitate, 0.99 for methyl stearate, and 1.0 for methyl oleate; the resolution, *R,* between methyl stearate and methyl oleate is not less than 1.5; and the relative standard deviation of the peak area responses for the palmitate and stearate peaks for replicate injections is not more than 6.0%. The relative standard deviation of the peak area response ratio of the palmitate to stearate peaks from these replicate injections is not more than 1.0%.

Procedure—Inject a volume (about 1 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas of the five major peaks for the methyl esters of the fatty acids, which elute in the following order: palmitate, stearate, oleate, linoleate, and linolenate. Calculate the relative ~~areas for these peaks~~ amounts of palmitate, stearate, oleate, linoleate, and linolenate, expressed as percentages of the total area of the five major peaks: for generic Oil, between 3% and 10% of methyl palmitate is found, between 2% and 8% of methyl stearate is found, between 14% and 24% of methyl oleate is found, between 63% and 73% of methyl linoleate is found, and between 0% and 3% of methyl linolenate is found; for mid-oleic Oil, between 2% and 9% of methyl palmitate is found, between 2% and 8% of methyl stearate is found, between 40% and 70% of methyl oleate is found, between 15% and 40% of methyl linoleate is found, and between 0% and 3% of methyl linolenate is found; and for high-oleic Oil, between 2% and 9% of methyl palmitate is found, between 2% and 8% of methyl stearate is found, between 70% and 90% of methyl oleate is found, between 5% and 15% of methyl linoleate is found, and between 0% and 3% of methyl linolenate is found.

Refractive index ⟨831⟩**:** between 1.472 and 1.474 at 20°.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

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Limit of peroxide—[NOTE—This test must be performed promptly after sampling to avoid oxidation of the test specimen.]

Solvent—Mix 60 mL of glacial acetic acid and 40 mL of chloroform.

Potassium iodide solution—Prepare a saturated solution of potassium iodide in freshly boiled and cooled water, and store it protected from light. [NOTE—Discard the solution if it becomes colored upon addition of *Solvent* and iodine-free starch TS.]

Procedure—Transfer about 10 g of Oil, accurately weighed, to a conical flask, add 30 mL of *Solvent*, and swirl to dissolve. Add 0.5 mL of *Potassium iodide solution*, swirl for 1.0 minute, add 30 mL of water, and titrate with 0.01 N sodium thiosulfate VS, with vigorous agitation, to a light yellow color. Add 2.0 mL of iodine-free starch TS, and continue the titration until the blue color has disappeared. Perform a blank determination, and make any necessary correction. Calculate the amount of peroxide, in mEq per kg, in the portion of Oil taken by the formula:

$$1000VN/W,$$

in which V is the volume, in mL, of sodium thiosulfate used in the titration; N is the actual normality of sodium thiosulfate VS; and W is the weight, in g, of Oil taken: not more than 10.0 mEq per kg is found.▲*NF24*

BRIEFING

Medium-Chain Triglycerides, *USP 28* page 3101. The proposed change in the Definition clarifies the source of the saturated fatty acids.

(EMC: E. Gonikberg) RTS—39838-1

Change to read:

» Medium-Chain Triglycerides ~~are obtained from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid ($C_8H_{16}O_2$) and of capric acid ($C_{10}H_{20}O_2$).~~

▲consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid ($C_8H_{16}O_2$) and capric acid ($C_{10}H_{20}O_2$). The fatty acids are derived from the oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineensis* Jacq.▲*NF24* They contain not less than 95 percent of saturated fatty acids with 8 and 10 carbon atoms.

In-Process Revision

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 28* page 2204, the *Fifth Interim Revision Announcement* on page 1559 of *PF* 30(5) [Sept.–Oct. 2004], *Sixth Interim Revision Announcement* on page 1965 of *PF* 30(6) [Nov.–Dec. 2004], page 793 of *PF* 26(3) [May–June 2000], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 3071 of *PF* 27(5) [Sept.–Oct. 2001], 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 710 of *PF* 29(3) [May–June 2003], page 1137 of *PF* 29(4) [July–Aug. 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 211 of *PF* 30(1) [Jan.–Feb. 2004], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 998 of *PF* 30(3) [May–June 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], and page 1674 of *PF* 30(5) [Sept.–Oct. 2004], and page 2092 of *PF* 30(6) [Nov.–Dec. 2004].

(HDQ) RTS—4173-4; 41987-2; 42000-1; 42028-3; 41807-2; 42030-1; 39417-2; 42048-2; 42048-1

Delete the following:

▲▲~~**USP Asparagine RS.**~~▲*USP28*▲*USP29*

Add the following:

▲**USP Asparagine Anhydrous RS**—[To come.]▲*USP29*

Add the following:

▲**USP Asparagine Monohydrate RS**—[To come.]▲*USP29*

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-benzazepine-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.▲*USP29*

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-benzazepine-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.▲*USP29*

Add the following:

▲**USP Benazepril Related Compound C RS** [3-[(1-carboxy-3-phenyl-1*S*-propyl)amino]-2,3,4,5-tetrahydro-2-oxo-(3*S*)-1*H*-1-benzazepine-1-acetic acid] ($C_{22}H_{24}N_2O_5$ ✧ 396.44—Dry portion in vacuum at 105° for 4 hours before using.▲*USP29*

Add the following:

■**USP Fluvastatin for System Suitability RS**—~~[fluvastatin sodium and fluvastatin sodium anti-isomer].~~▲It is a mixture of fluvastatin sodium and three related impurities: fluvastatin anti-isomer, fluvastatin hydroxydiene, and fluvastatin *t*-butyl ester.

Fluvastatin anti-isomer [*R*,R*,E*]-(±)-7-[3-(4-fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt.

Fluvastatin hydroxydiene [*E,E*]-(±)-7-[3-(4-fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-hydroxy-4,6-heptadienoic acid monosodium salt.

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Fluvastatin t-butyl ester [*R**,*S**,*E*]-(±)-7-[3-(4-fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-4,6-heptenoic acid 1,1-dimethylethyl ester.▲*USP29*■1S *(USP29)*

Change to read:

USP Gabapentin Related Compound A RS ~~**[**3,3 pentamethylene 5 butyrolactam**]**~~

▲**[**2-aza-spiro[4.5]decan-3-one**]**▲*(USP29)*
($C_9H_{15}NO$ ✧ 153.22)—Do not dry. Keep container tightly closed.

Add the following:

▲**USP Gabapentin Related Compound B RS [**(1-cyanocyclohexyl)-acetic acid**]** $C_9H_{13}NO_2$ ✧ 167.21)—[To come.]▲*USP29*

Add the following:

▲**USP Gabapentin Related Compound D RS [**[1-(3-oxo-2-aza-spiro[4.5]dec-2-ylmethyl)-cyclohexyl)-acetic acid**]** ($C_{18}H_{29}NO_3$ ✧ 307.43)—[To come.]▲*USP29*

Add the following:

▲**USP Gabapentin Related Compound E RS [**carboxymethyl-cyclohexanecarboxylic acid**]** ($C_9H_{14}O_4$ ✧ 186.21)—[To come.]▲*USP29*

Add the following:

▲**USP Isomalt RS**—[To come.]▲*USP29*

Add the following:

▲**USP Meloxicam RS**—[To come.]▲*USP29*

Add the following:

▲**USP Meloxicam Related Compound A RS [**4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid ethylester 1,1-dioxide**]**—[To come.]▲*USP29*

Add the following:

▲**USP Meloxicam Related Compound B RS [**2-amino-5-methyl-thiazole**]**—[To come.]▲*USP29*

Add the following:

▲**USP Meloxicam Related Compound C RS [**isopropyl-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide**]**—[To come.]▲*USP29*

Add the following:

▲**USP Meloxicam Related Compound D RS [**4-methoxy-2-methyl-*N*-(5-methyl-1,3-thiazole-2yl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide**]**—[To come.]▲*USP29*

Add the following:

▲**USP Oxandrolone Related Compound A RS [**(7,8-didehydro-oxandrolone) or (17*β*-hydroxy-17α-methyl-2-oxa-5α-androst-7-en-3-one)**]**.▲*USP29*

Add the following:

▲**USP Oxandrolone Related Compound B RS [**(anhydro-oxandrolone) or (17*β*-17dimethyl-2-oxa-18-nor-5α-androstan-3-one)**]**.▲*USP29*

Add the following:

▲**USP Paroxetine Hydrochloride for System Suitability RS**—Mixture of 1% paroxetine related compound A **[**piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3 *S-trans*); and 1% of paroxetine related compound B [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl)-, hydrochloride (3 *S-trans*)]**]** in a matrix of paroxetine hydrochloride.▲*USP29*

Add the following:

▲**USP Tiamulin RS**—[To come.]▲*USP29*

Add the following:

▲**USP Ubidecarenone Related Compound A RS [**coenzyme Q_9**]**—[To come.]▲*USP29*

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GENERAL CHAPTERS

General Information

BRIEFING

⟨**1075**⟩ **Good Compounding Practices,** *USP 28* page 2620. It is proposed to revise this general chapter to improve its readability and to provide definitions for terms used in several sections. The word "levels" has been replaced with "categories," and the previous levels 1–3 have been combined to form category 1. There are now 7 categories, as follows.

1. Nonsterile—Simple
2. Nonsterile—Complex
3. Sterile—Risk Level 1 and Ophthalmics, Nasal, Oral Inhalation, etc.
4. Sterile—Risk Level 2
5. Sterile—Risk Level 3
6. Radiopharmaceuticals
7. Veterinary

On the basis of comments received, the Committee has voted to delete the section *Compounding Pharmacy Generated Products* and to redefine a compounder as "a professional authorized by the state to perform compounding."

In addition, other revisions were proposed to clarify the intent of the chapter.

(CRX: C. Okeke) RTS—37469-19

⟨1075⟩ GOOD COMPOUNDING PRACTICES

Change to read:

The purpose of this chapter is to provide compounders with guidance on applying good compounding practices for the preparation of compounded formulations for dispensing and/or administration to humans or animals.

▲This chapter is intended to provide information as a supplement to other relevant chapters. The following discussion is applicable to those engaged in compounding preparations in all pharmacies.▲*USP29*

It is expected that pharmacists or compounders engaged in the compounding of drugs will compound in conformance with applicable state and federal compounding laws, regulations, or guidelines.

Change to read:

APPLICABLE DEFINITIONS

Compounding (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩)—Compounding involves the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner's prescription

▲of medication order▲*USP29*
under an initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice. Compounding includes the following:

a. Preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.
b. Reconstitution

▲or manipulation▲*USP29*
of commercial products that may require the addition of ~~two~~

▲one▲*USP29*
or more ingredients as a result of a licensed practitioner's prescription drug order.

~~c. Manipulation of commercial products that may require the addition of one or more ingredients as a result of a licensed practitioner's prescription drug order.~~
~~d. Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.~~

▲e. Preparation of drugs or devices for the purposes of, or as an incident to, research, teaching, or chemical analysis.▲*USP29*

~~**Levels of Compounding**~~

~~Level 1~~	~~Nonsterile (topical)~~ ~~Mixing of one or two creams~~ ~~Mixing of creams with alcohol, water, etc. (as per manufacturer's labeling instruction)~~
~~Level 2~~	~~Nonsterile (topical)~~ ~~Preparation of nonsterile topical ointment, cream Preparations with no dosage limitation~~
~~Level 3~~	~~Nonsterile (reconstituting or flavoring)~~ ~~Reconstitution according to manufacturer's labeling instruction Addition of flavoring~~
~~Level 4~~	~~Sterile (simple injections, e.g., reconstituted for immediate administration) Preparation of injections for immediate administration~~
~~Level 5~~	~~Nonsterile (dosage forms)~~ ~~Preparation of solid oral dosage forms (tablets, capsules)~~ ~~Preparation of liquid oral dosage forms (emulsion, solutions, suspensions, etc.)~~ ~~Preparation of suppositories, lozenges~~
~~Level 6~~	~~Sterile (ophthalmics/otics) Preparation of ophthalmic and otic suspensions, solutions~~

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~~Level 7~~	~~Sterile (complex injections) Preparation of injections for many patients Preparation of injection not for immediate administration Preparation of total parenteral nutritions (TPNs) Preparation of multicomponent injection~~
~~Level 8~~	~~Other sterile injections and patches Preparation of chemotherapeutic injections or implants Preparation of transdermal medications~~
~~Level 9~~	~~Sterile (radiopharmaceuticals) Preparation of radiopharmaceuticals~~

▲**Categories of Compounding—**The categories of compounding are intended to provide an understanding among compounders when different forms of preparations are compounded. It is to be understood that there are levels of training associated with each category. In the categories of compounding described below, certain criteria were used to determine the overall classification.

Category 1	Nonsterile—Simple Generally, the mixing of two or more commercial products
Category 2	Nonsterile—Complex Generally, compounding with the bulk drug substances or when calculations are required.
Category 3	Sterile—Risk Level 1 (See *Low-Risk Level* in USP general chapter ⟨797⟩)
Category 4	Sterile—Risk Level II (See *Medium-Risk Level* in USP general chapter ⟨797⟩)
Category 5	Sterile—Risk Level III (See *High-Risk Level* in USP general chapter ⟨797⟩)
Category 6	Radiopharmaceuticals Preparation of radiopharmaceuticals
Category 7	Veterinary Preparation of veterinary pharmaceuticals▲*USP29*

Manufacturing—Manufacturing involves the production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis. Manufacturing also includes (1) any packaging or repackaging of the substance(s) or labeling or relabeling of containers for the promotion and marketing of such drugs or devices; (2) any preparation of a drug or device that is given or sold for resale by pharmacies, practitioners, or other persons; (3) the distribution of inordinate amounts of compounded preparations or the copying of commercially available drug products; and (4) the preparation of any quantity of a drug product without a licensed prescriber/patient/licensed pharmacist/compounder relationship.

Component—A component is any ingredient used in the compounding of a drug product, including any that are used in its preparation, but may not appear on the labeling of such a product. (See *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ for additional definitions.)

~~**Pharmacy Generated Product (PGP)—**A pharmacy generated product (PGP) is a product that is prepared, packaged, and labeled in a pharmacy and can be sold by the pharmacy without a prescription. PGPs are clearly different from drugs defined in section 201 (g) of the Federal Food, Drug, and Cosmetic Act.~~

▲▲*USP29*

Compounder—A compounder is a ~~pharmacist or a physician who is engaged in the act of compounding~~

▲professional authorized by the state to perform compounding▲*USP29*
pursuant to a precription order by a licensed prescriber.

Change to read:

RESPONSIBILITIES OF THE COMPOUNDER

a. Compounders who are engaged in drug compounding or nutriceutical compounding shall be proficient in compounding and should continually expand their compounding knowledge by participating in seminars and/or studying appropriate literature.

b. A compounder ~~shall~~

▲must▲*USP29*
be familiar with all of the details of *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩,

▲*Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩,▲*USP29*

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and other applicable state or federal compounding guidelines or laws. In addition, the compounder ~~shall~~

▲must▲*USP29*
be responsible for the following:

- certifying all prescription orders;
- approving or rejecting all components, drug product containers, closures, in-process materials, and labeling;
- preparing and reviewing all compounding records to assure that errors have not occurred in the compounding process;
- assuring the proper maintenance, cleanliness, and use of all equipment used in a prescription compounding practice;
- assuring that only ~~personnel authorized by the compounding supervisor shall~~

  ▲authorized personnel shall ▲*USP29*
  be in the immediate vicinity of the drug compounding operations;
- assuring that the drug product and components of drug products are not on the list of federally recognized drug products that have been withdrawn or removed from the market for public health reasons.

c. The compounder ~~shall~~

▲must▲*USP29*
ensure that personnel engaged in compounding wear clean clothing appropriate to the type of compounding performed, e.g., coats, gowns, gloves, masks, shoes, aprons, or other items as needed for protection of personnel from chemical exposures and for prevention of drug contamination.

d. The compounder ~~shall~~

▲must▲*USP29*
implement procedures to prevent cross-contamination when compounding with drugs (e.g., penicillins) that require special precaution to prevent cross-contamination.

Change to read:

TRAINING

All personnel involved in the compounding, evaluation, packaging, and dispensing of compounded preparations shall be properly trained for the type of compounding conducted. All training activities will be covered by appropriate standard operating procedures (SOPs) and documentation.

All compounders and all personnel involved in compounding must be well trained and must participate in current, relevant training programs. It is the responsibility of the ~~pharmacist~~

▲compounder▲*USP29*
to ensure that a training program has been implemented and that it is ongoing. Standards of ~~pharmacy~~

▲▲*USP29*
practice require that all employees be adequately trained in their job functions and that all of the training is properly documented. Steps in the training procedure will include the following:

a. All employees involved in pharmaceutical compounding shall read and become familiar with *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩.
b. All employees shall read and become familiar with each of the procedures related to compounding, including those involving the facility, equipment, personnel, actual compounding, evaluation, packaging, storage, and dispensing.
c. The compounder shall meet with employees to review their work and answer any questions the employees may have concerning SOPs.
d. The compounder shall demonstrate the procedures for the employee, and will observe and guide the employee throughout the ~~procedure.~~

   ▲training process.▲*USP29*
   The employee will then repeat the procedure without any assistance from, but under the

   ▲direct▲*USP29*
   supervision of, the ~~pharmacist~~

   ▲compounder.▲*USP29*
e. When the employee has demonstrated to the compounder a verbal and functional knowledge of the procedure, then and only then, will the employee be permitted to perform the procedure without

   ▲direct▲*USP29*
   supervision.

   ▲However, the compounder should be physically present and should check off the final preparation.▲*USP29*
f. When the compounder is satisfied with the employee's knowledge and proficiency, the compounder will sign off on the documentation records to show that ~~both the employee and the compounder agree.~~

   ▲the employee was appropriately trained.▲*USP29*
g. The compounder shall continually monitor the work of the employee and

   ▲assure that the employee's calculations and work are accurate and adequately performed. The compounder is completely responsible for the finished preparation.

   The compounder will▲*USP29*
   answer any questions the employee may have concerning the SOPs.

Change to read:

PROCEDURES AND DOCUMENTATION

All significant procedures performed in the compounding area will be covered by SOPs and will be documented.

Procedures should be developed for the facility, equipment, personnel, preparation, packaging, and storage of compounded preparations to ensure accountability, accuracy, quality, safety (including access to Material Safety Data Sheets) and uniformity in ~~a compounding practice. More importantly,~~

▲compounding.▲*USP29*

Implementing SOPs establishes procedural consistency and also provides a reference for orientation and training of personnel.

Documentation enables a ~~pharmacy~~

▲compounder,▲*USP29*
whenever necessary, to systematically trace, evaluate, and replicate the steps included throughout the preparation process of a compounded ~~product.~~

▲preparation.▲*USP29*

Change to read:

DRUG COMPOUNDING FACILITIES

a. Compounding facilities shall have an adequate space that is specifically designated for compounding of prescriptions. This area may include a space for the storage of equipment and materials.
b. Sterile compounded preparations shall be compounded in accordance with the provisions in *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and aseptic processes shall be conducted in an area separate and distinct from the area used for the compounding of nonsterile products.
c. The areas used for compounding shall be maintained in clean, orderly, and sanitary conditions.
d. The areas for drug compounding shall be maintained in a good state of repair. The plumbing system shall be free of defects that could contribute to contamination of any compounded product. Adequate washing facilities shall be easily accessible to the compounding areas. Such facilities shall include, but not be limited to, hot and cold water, soap or detergent, and an air-drier or single-use towels.
e. Potable water shall be supplied under continuous positive pressure.
f. The area for compounding shall have adequate lighting and ventilation.
g. The area for compounding shall be free of infestation by insects, rodents, and other vermin. Trash shall be held and disposed of in a sanitary and timely manner.
h. Sewage and other refuse in the area of compounding shall be disposed of in a safe and sanitary manner.
i. Bulk drugs and other chemicals or materials used in the compounding of drugs must be stored as directed by the manufacturer, or according to USP monograph requirements, in a clean, dry area, ~~(defined temperature condition), or in a refrigerator or freezer as specified.~~

▲under appropriate temperature conditions (controlled room temperature, refrigerator, or freezer).▲*USP29*
The bulk chemicals shall be stored in a manner such that they are protected from contamination. All containers shall be properly labeled.
j. If parenteral products are compounded, the compounder shall refer to *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and *Injections* ⟨1⟩ for compounding technique applications.

Change to read:

DRUG COMPOUNDING EQUIPMENT

(See also *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.)

a. The equipment or utensils used for compounding of a drug ~~product~~

▲preparation▲*USP29*
shall be of appropriate design and capacity. The equipment ~~shall~~

▲should▲*USP29*
be stored in such a manner as to protect it from contamination, and shall be located in such a place as to facilitate operations for its use, maintenance, and cleaning.
b. ~~The equipment shall be cleaned and sanitized prior to use to prevent contamination that may affect the safety or quality of compounded preparations.~~

▲
▲*USP29*
c. The equipment ~~shall~~

▲should▲*USP29*
be of suitable composition such that the surfaces that contact components are neither reactive, additive, nor absorptive and therefore will not affect or alter the purity of the compounded preparations.
d. Automated, mechanical, electronic, and other types of equipment used in compounding ~~shall~~

▲or testing of compounded preparations should▲*USP29*
be routinely inspected, calibrated as necessary, and checked to ensure proper performance.
e. Immediately prior to initiation of compounding operations, the equipment shall be inspected by the compounder to determine its suitability for use.
f. ~~The equipment shall be cleaned appropriately using special instructions when cross-contaminating products or products requiring special precaution.~~

▲After use, the equipment should be appropriately cleaned. Extra care should be used when cleaning equipment used in compounding preparations requiring special precaution.▲*USP29*
e.g., antibiotics, cytotoxins, cancer drugs, and other hazardous materials. ~~, are used with the equipment~~

▲
▲*USP29*
If possible, special equipment may be dedicated for such use or if the same equipment is being used for all drug products, appropriate procedures must be in place to allow meticulous cleaning of equipment prior to use with other drugs.

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Change to read:

COMPONENT SELECTION REQUIREMENTS

a. The compounder ~~shall~~

▲must▲*USP29*
first attempt to use *USP–NF* drug substances manufactured in an FDA-registered facility.

b. The compounder shall also first attempt to use inactive components manufactured in an FDA-registered facility.
c. If components are not obtainable from an FDA-registered facility or if the FDA and/or the providing company cannot document FDA registration, compounders shall use their professional judgment in first receiving, storing, or using the components that meet official compendial requirements or are provided by another high quality source.
d. If components of compendial quality are not obtainable, components of high quality such as those that are chemically pure, analytical reagent grade, American Chemical Society-certified, or Food Chemical Codex grade may be used.
e. When a component is not obtained from an official compendial source or is not obtainable from the sources mentioned above, the component may be obtained from a source deemed acceptable and reliable in the professional judgment of the compounder.
f. When a component is derived from ruminant animals (e.g., bovine, caprine, ovine) the supplier shall provide written assurance that these animals were born, raised, ~~or~~

▲and▲*USP29*
slaughtered in countries where bovine spongiform encephalopathy (BSE) and scrapie are known not to exist.

g. The compounder shall not use components that are listed by FDA to be withdrawn from the market for public health reasons.
h. Components shall be stored off the floor, handled and stored to prevent contamination, and rotated so that the oldest stock is used first.

Change to read:

PACKAGING AND DRUG ~~PRODUCT~~

▲PREPARATION▲*USP29* CONTAINERS

a. The compounder shall ensure that the containers and container closures used in packaging the compounded preparations meet the requirements under *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩. The compounder shall obtain written records from the supplier to show that the containers meet USP requirements.
b. Containers and container closures intended for compounding of sterile preparations and nonsterile preparations must be handled, sterilized (if appropriate), and stored as described in *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩ and *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. The use of commercially available presterilized containers ~~may be considered.~~

▲is encouraged for sterile preparations.▲*USP29*

c. The containers and closures shall be stored off the floor, handled and stored to prevent contamination, and rotated so that the oldest ~~approved~~

▲▲*USP29*
stock is used first.

d. The containers and container closures shall be stored in such a way as to permit inspection and cleaning of the work area.
e. The containers and container closures shall be made of clean materials that are neither reactive, additive, nor absorptive.
f. The containers and closures shall be of suitable material so as not to alter the quality, strength, or purity of the compounded drug.
g. The compounder shall ensure that the containers and container closures selected to dispense the finished compounded prescription, whether sterile or nonsterile or radiopharmaceutical, meet the criteria in sections (a)–(f) above.

Change to read:

COMPOUNDING CONTROLS

a. The compounder ~~shall~~

▲should▲*USP29*
ensure that there are written procedures for the compounding of drug products to assure that the finished products have the identity, strength, quality, and purity that they purport to have.

▲These procedures should be available in either written form or electronically stored with printable documentation.▲*USP29*

b. The compounder shall establish procedures ~~for listing components, their amounts (weight or volume), the order of component mixing, and a description of the compounding process~~

▲that include a description of (1) components, their amounts, the order of component additives, and the compounding process; (2) the required equipment and utensils; and (3) the drug product container and closure system.▲*USP29*

~~c. The compounder shall list all equipment, utensils, and container closure systems relevant to the sterility, stability, and intended use of a drug.~~

▲▲*USP29*

d. The written procedures described above shall be followed in execution of the compounding process.
e. The compounder shall accurately weigh, measure, and subdivide as appropriate.
f. The compounder shall check and recheck each procedure at each stage of the process to ensure that each weight or measure is correct as stated in the written compounding procedures.
g. If a component is transferred from the original container to another container (e.g., a powder is taken from the original container, weighed, placed in a container, and stored in that other container), the new container shall be identified with

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the component name, weight or measure, the lot or control number, the expiration or beyond-use date, and the transfer date.

~~h. The compounder shall have drug compounding procedures available in either written form or electronically stored with printable documentation.~~

~~i. The procedures shall include a description of (1) the components, their amounts, the order of component additives, and the compounding process; (2) the required equipment and utensils; and (3) the drug product container and closure system.~~

▲▲*USP29*

j. The compounder ~~shall~~

▲should▲*USP29*
have established written procedures that will describe the tests or examinations to be conducted on the ~~product~~

▲preparation▲*USP29*
compounded (e.g., the degree of weight variation among capsules) to assure uniformity and integrity of compounded drug ~~products.~~

▲preparations.▲*USP29*

k. Appropriate control procedures ~~shall~~

▲should▲*USP29*
be established to monitor the output and to validate the performance of those compounding processes that may be responsible for causing variability in the final compounded preparations. Factors that may cause variability include (1) capsule weight variation; (2) adequacy of mixing to assure uniformity and homogeneity; and (3) clarity, completeness, or pH of solutions.

l. Appropriate written procedures ~~shall~~

▲should▲*USP29*
be designed to prevent microbiological contamination of compounded drug ~~products~~

▲preparations▲*USP29*
purporting to be sterile, and these procedures shall be followed. Such procedures shall include validation of sterilization processes (see *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩).

m. The compounder ~~shall~~

▲should▲*USP29*
establish appropriate beyond-use dates determined either from available *USP–NF* monographs, appropriate testing, or from peer-reviewed literature.

n. The compounder ~~shall~~

▲should▲*USP29*
adopt appropriate storage requirements as provided in *Preservation*, *Packaging*, *Storage*, *and Labeling* under *General Notices and Requirements*.

Change to read:

LABELING

1. The compounder's ~~prescription label shall contain the following:~~

▲preparation label should contain information required by state and federal law and accepted standards of practice.▲*USP29*

~~a Patient's name~~
~~b Prescriber's name~~
~~c Name and address of compounder~~
~~d Prescription number~~
~~e Established name or distinct common name (cannot use trademarked name of a manufactured product)~~
~~f Strength~~
~~g Statement of quantity~~
~~h Directions for use~~
~~i Date filled~~
~~j Beyond-use date/storage, etc.~~
~~k An appropriate designation that this is a compounded prescription~~
~~l. Any other federal or state requirements [NOTE—The compounder shall not use an NDC number assigned to another product.]~~

▲[NOTES—(a) The compounder shall use the established name or distinct common name (cannot use the trademarked name of a manufactured product). (b) The compounder cannot indicate that the compounded product is therapeutically equivalent to a manufactured product. (c) The label should state that this is a compounded preparation. (d) The compounder shall not use an NDC number assigned to another product.]▲*USP29*

2. The compounder shall label any excess compounded products so as to reference them to the formula used, the assigned control number, and beyond-use date based on the compounder's appropriate testing, published data, or *USP–NF* standards.

3. ~~Products prepared~~

▲Preparations compounded▲*USP29*
in anticipation of a prescription prior to receiving a valid prescription should not be prepared in an inordinate amount. A regularly used amount should be prepared on the basis of a history of prescriptions filled by the pharmacy. These ~~products shall~~

▲preparations should▲*USP29*
be labeled or documentation referenced with the following:

a. A complete list of ingredients or preparation name and reference or established name or distinct common name
b. Dosage form
c. Strength
d. Preparation date

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e. Name and address of compounder
f. Inactive ingredients
g. Batch or lot number
h. Assigned beyond-use date, based on published data, or appropriate testing, or *USP–NF* standards.

Storage conditions for these ~~products shall~~

▲preparations should▲*USP29*
be dictated by their composition and sterility, e.g., stored in a clean, dry place ~~(defined temperature condition), in a refrigerator, or at controlled room temperature.~~

▲under appropriate temperature conditions (controlled room temperature, refrigerator, or freezer.)▲*USP29*

4. The compounder ~~shall~~

▲should▲*USP29*
examine the ~~product~~

▲preparation▲*USP29*
for correct labeling after completion of the compounding process.

Change to read:

RECORDS AND REPORTS

a. The compounder shall maintain records, including but not limited to, the hard copy of the prescription to indicate that the prescription is compounded,

▲and to provide formulation records and compounding records.▲*USP29*
b. The compounder shall keep adequate records of controlled drug substances (scheduled drugs) used in compounding.
c. All records of all compounded ~~products~~

▲preparations▲*USP29*
shall be kept for a period of time as set forth in the

▲federal and▲*USP29*
state laws or regulations. Such records shall be readily available for authorized inspection.

▲d. The compounding records shall include the manufacturer and lot number of all ingredients.▲*USP29*

Change to read:

COMPOUNDING FOR A PRESCRIBER'S OFFICE USE

a. Compounders may prepare compounded drug ~~products~~

▲preparations▲*USP29*
for a prescriber's office use ~~pursuant to federal and state requirements.~~

▲only where permitted by federal and state requirements.▲*USP29*
b. An order by the prescriber indicating the formula and quantity ordered may be filled in the compounder's facility.
c. ~~The~~

▲Where compounding for office use is permitted, the▲*USP29*
compounder shall compound the ~~product for the~~

▲preparation for the sole▲*USP29*
purpose of administration by or for the prescriber.
d. A record of the compounding process shall be maintained.
e. A label ~~may~~

▲must▲*USP29*
be generated and a number may be assigned.

Change to read:

COMPOUNDING VETERINARIAN PRODUCTS

a. Compounders shall compound prescriptions for animals on the basis of prescription orders.
b. These prescriptions shall be handled and filled ~~as are human prescriptions.~~

▲according to the guideline available for compounding of veterinarian products.▲*USP29*

Delete the following:

▲~~COMPOUNDING PHARMACY GENERATED PRODUCTS~~

~~a Compounders may prepare compounded drug products that can be sold without a prescription.~~
~~b Pharmacy-generated products (PGP) shall be compounded using the same procedures as those for prescription drug products detailed in this chapter.~~
~~c Additional labeling sufficient for patient use will be required to meet the individual State Board of Pharmacy and federal requirements. [NOTE—PGPs are clearly different from drugs defined in section 201 (g) of the Federal Food, Drug, and Cosmetic Act.]~~▲*USP29*

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REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Methyl Red. It is proposed to add this new reagent.

(HDQ: M. Marques) RTS—41930-1

Add the following:

▲**Methyl Red** *(2-[4-dimethylaminophenylazo]benzoic acid, C. I. Acid Red 2)* $C_{15}H_{15}N_3O_2$—**269.30**—Use ACS reagent grade.▲*USP29*

BRIEFING

1-Vinyl-2-pyrrolidone, *USP 28* page 2850. It is proposed to modify the name of this reagent to be in accordance with the name in the appropriate monograph. Also, synonyms and the CAS number are being added to facilitate the procurement of this reagent.

(HDQ: M. Marques) RTS—41930-2

Change to read:

~~**1-Vinyl-2-pyrrolidone**~~

▲**Vinylpyrrolidinone** (*1-Vinyl-2-pyrrolidinone, 1-vinyl-2-pyrrolidone, N-vinylpyrrolidinone, N-vinylpyrrolidone*),▲*USP29*
C_6H_9NO—**111.14**

▲[*88-12-0*]▲*USP29*
—Colorless liquid.

Assay—Inject an appropriate volume into a 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 0.25-mm × 30-m capillary column coated with a 1-µm layer of G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the C_6H_9NO peak is not less than 99.0% of the total peak area.

Water, Method I ⟨921⟩: not more than 0.1%, determined on 2.5 g, using a mixture of 50 mL of methanol and 10 mL of butyrolactone as the solvent.

▲[NOTE—A suitable grade is available from http://www.sigma-aldrich.com, catalog number V340-9.]▲*USP29*

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 28* page 2862 and page 2170 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to add a new volumetric solution, 0.1 N Lithium Methoxide in Methanol.

(HDQ: M. Marques) RTS—41932-1

Change to read:

Ammonium Thiocyanate, Tenth-Normal (0.1 N)
NH_4SCN, **76.12**
7.612 g in 1000 mL

Dissolve about 8 g of ammonium thiocyanate in 1000 mL of water, and standardize the solution as follows.

Accurately measure about 30 mL of 0.1 N silver nitrate VS into a glass-stoppered flask. Dilute with 50 mL of water, then add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS, and titrate with the ammonium thiocyanate solution to the first appearance of a red-brown color. ~~Calculate the normality.~~

$$\blacksquare N = \frac{\text{mL } AgNO_3 \times N\,AgNO_3}{\text{mL } NH_4SCN \text{ Solution}}\ \blacksquare 1S\ (USP28)$$

If desirable, 0.1 N ammonium thiocyanate may be replaced by 0.1 N potassium thiocyanate where the former is directed in various tests and assays.

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Change to read:

Bromine, Tenth-Normal (0.1 N)
Br, **79.90**
7.990 g in 1000 mL

Dissolve 3 g of potassium bromate and 15 g of potassium bromide in water to make 1000 mL, and standardize the solution as follows.

Accurately measure about 25 mL of the solution into a 500-mL iodine flask, and dilute with 120 mL of water. Add 5 mL of hydrochloric acid, insert the stopper in the flask, and shake it gently. Then add 5 mL of potassium iodide TS, again insert the stopper, shake the mixture, allow it to stand for 5 minutes, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. ~~Calculate the normality.~~

■ ■1S (*USP28*)

Preserve in dark amber-colored, glass-stoppered bottles.

$$\blacksquare N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{\text{mL } Br_2 \text{ Solution}} \blacksquare 1S\ (USP28)$$

Change to read:

Ceric Ammonium Nitrate, Twentieth-Normal (0.05 N)
$Ce(NO_3)_4 \cdot 2NH_4NO_3$, **548.22**
2.741 g in 100 mL

Dissolve 2.75 g of ceric ammonium nitrate in 1 N nitric acid to obtain 100 mL of solution, and filter. Standardize the solution as follows.

Accurately measure 10 mL of freshly standardized 0.1 N ferrous ammonium sulfate VS into a flask, and dilute with water to about 100 mL. Add 1 drop of nitrophenanthroline TS, and titrate with the ceric ammonium nitrate solution to a colorless endpoint. ~~From the volume of 0.1 N ferrous ammonium sulfate VS taken and the volume of ceric ammonium nitrate solution consumed, calculate the normality.~~

$$\blacksquare N = \frac{\text{mL } Fe(NH_4)_2(SO_4)_2 \times \text{N } Fe(NH_4)_2(SO_4)_2}{\text{mL } Ce(NO_3)_4 \cdot 2NH_4NO_3} \blacksquare 1S\ (USP28)$$

Change to read:

Ceric Sulfate, Tenth-Normal (0.1 N)
$Ce(SO_4)_2$, **332.24**
33.22 g in 1000 mL

~~Transfer 59 g of ceric ammonium nitrate to a beaker, add 31 mL of sulfuric acid, mix, and cautiously add water, in 20-mL portions, until solution is complete. Cover the beaker, allow to stand overnight, filter through a fine-porosity, sintered-glass crucible, dilute with water to 1000 mL, and mix.~~

■Use commercially available volumetric standard solution.■1S (*USP28*)

Standardize the solution as follows. ~~[NOTE—Prepare the osmium tetroxide solution used in this procedure in a well-ventilated hood, as poisonous vapors are given off by this compound.] Weigh accurately 200 mg of arsenic trioxide, previously dried at 105° for 1 hour, and transfer to a 500-mL conical flask. Wash down the inner walls of the flask with 25 mL of sodium hydroxide solution (2 in 25), swirl to dissolve the substance, and when solution is complete, add 100 mL of water, and mix. Add 10 mL of dilute sulfuric acid (1 in 3), then add 2 drops each of orthophenanthroline TS and a 1 in 400 solution of osmium tetroxide in 0.1 N sulfuric acid, and slowly titrate with the ceric sulfate solution until the pink color is changed to a very pale blue. Calculate the normality. Each 4.946 mg of arsenic trioxide is equivalent to 1 mL of 0.1 N ceric sulfate.~~

■Accurately weigh about 0.2 g of sodium oxalate, primary standard, previously dried for 2 hours at 105°, and dissolve in 75 mL of water. Add, with stirring, 2 mL of sulfuric acid that has previously been mixed with 5 mL of water, mix well, add 10 mL of hydrochloric acid, and heat to between 70° and 75°. Titrate with 0.1 N ceric sulfate to a permanent slight yellow color. Each 6.700 mg of sodium oxalate is equivalent to 1 mL of 0.1 N ceric sulfate.

$$\blacksquare N = \frac{\text{mg } Na_2C_2O_4}{67.00 \times \text{mL } Ce(SO_4)_2 \text{ solution}} \blacksquare 2S\ (USP28)$$

Change to read:

Cupric Nitrate, Tenth-Normal (0.1 N)
$Cu(NO_3)_2 \cdot 2.5H_2O$, **232.59**
23.26 g in 1000 mL
$Cu(NO_3)_2 \cdot 3H_2O$, **241.60**
24.16 g in 1000 mL

Dissolve 23.3 g of cupric nitrate 2.5 hydrate, or 24.2 g of the trihydrate, in water to make 1000 mL. Standardize the solution as follows.

Transfer 20.0 mL of the solution to a 250-mL beaker. Add 2 mL of 5 M sodium nitrate, 20 mL of ammonium acetate TS, and sufficient water to make 100 mL. Titrate with 0.05 M edetate disodium VS. Determine the endpoint potentiometrically using a cupric ion-

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double junction reference electrode system. Perform a blank determination, and make any necessary correction. ~~Calculate the normality by the formula:~~

~~$VM / 20.0$,~~

~~in which V is the volume, in mL, of edetate disodium consumed, M is the molarity of the edetate disodium, and 20.0 is the number of mL of cupric nitrate solution taken.~~

$$N = \frac{\text{mL edetate disodium (corrected for the blank)} \times \text{M edetate disodium}}{20.0}$$ ■1S (*USP28*)

15 mL of sodium hydroxide TS and 300 mg of hydroxy naphthol blue, and continue the titration with the edetate disodium solution to a blue endpoint. ~~Calculate the molarity taken by the formula:~~

~~$W / (100.09V)$,~~

~~in which W is the weight, in mg, of $CaCO_3$ in the portion of calcium carbonate taken, and V is the volume, in mL, of edetate disodium solution consumed.~~

$$M = \frac{(\text{g } CaCO_3)(1000)}{100.09 \times \text{mL EDTA}}$$ ■1S (*USP28*)

Change to read:

Standard Dichlorophenol-Indophenol Solution

To 50 mg of 2,6-dichlorophenol-indophenol sodium that has been stored in a desiccator over soda lime add 50 mL of water containing 42 mg of sodium bicarbonate, shake vigorously, and when the dye is dissolved, add water to make 200 mL. Filter into an amber glass-stoppered bottle.

■Use within 3 days, and standardize immediately before use.■1S (*USP28*)

Standardize the solution as follows.

Accurately weigh 50 mg of USP Ascorbic Acid RS, and transfer to a glass-stoppered, 50-mL volumetric flask with the aid of a sufficient volume of metaphosphoric-acetic acids TS to make 50 mL. Immediately transfer 2 mL of the ascorbic acid solution to a 50-mL conical flask containing 5 mL of the metaphosphoric-acetic acids TS, and titrate rapidly with the dichlorophenol-indophenol solution until a distinct rose-pink color persists for at least 5 seconds. Perform a blank titration by titrating 7 mL of the metaphosphoric-acetic acids TS plus a volume of water equal to the volume of the dichlorophenol solution used in titrating the ascorbic acid solution. Express the concentration of the standard solution in terms of its equivalent in mg of ascorbic acid.

Change to read:

Edetate Disodium, Twentieth-Molar (0.05 M)
$C_{10}H_{14}N_2Na_2O_8 \cdot 2H_2O$, **372.24**
18.61 g in 1000 mL

Dissolve 18.6 g of edetate disodium in water to make 1000 mL, and standardize the solution as follows.

Accurately weigh about 200 mg of chelometric standard calcium carbonate, previously dried at 110° for 2 hours and cooled in a desiccator, transfer to a 400-mL beaker, add 10 mL of water, and swirl to form a slurry. Cover the beaker with a watch glass, and introduce 2 mL of diluted hydrochloric acid from a pipet inserted between the lip of the beaker and the edge of the watch glass. Swirl the contents of the beaker to dissolve the calcium carbonate. Wash down the sides of the beaker, the outer surface of the pipet, and the watch glass with water, and dilute with water to about 100 mL. While stirring the solution, preferably with a magnetic stirrer, add about 30 mL of the edetate disodium solution from a 50-mL buret. Add

Change to read:

Ferric Ammonium Sulfate, Tenth-Normal (0.1 N)
$FeNH_4(SO_4)_2 \cdot 12H_2O$, **482.19**
48.22 g in 1000 mL

Dissolve 50 g of ferric ammonium sulfate in a mixture of 300 mL of water and 6 mL of sulfuric acid, dilute with water to 1000 mL, and mix. Standardize the solution as follows:

Accurately measure about 40 mL of the solution into a glass-stoppered flask, add 5 mL of hydrochloric acid, mix, and add a solution of 3 g of potassium iodide in 10 mL of water. Insert the stopper, allow to stand for 10 minutes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents. ~~and calculate the normality.~~

■■1S (*USP28*)

Store in tight containers, protected from light.

$$N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{\text{mL } FeNH_4(SO_4)_2}$$ ■1S (*USP28*)

Change to read:

Ferrous Ammonium Sulfate, Tenth-Normal (0.1 N)
$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$, **392.14**
39.21 g in 1000 mL

Dissolve 40 g of ferrous ammonium sulfate in a previously cooled mixture of 40 mL of sulfuric acid and 200 mL of water, dilute with water to 1000 mL, and mix. On the day of use, standardize the solution as follows.

Accurately measure 25 to 30 mL of the solution into a flask, add 2 drops of orthophenanthroline TS, and titrate with 0.1 N ceric sulfate VS until the red color is changed to pale blue. ~~From the volume of 0.1 N ceric sulfate consumed, calculate the normality.~~

$$N = \frac{\text{mL } Ce^{IV} \times \text{N } Ce^{IV}}{\text{mL } Fe^{II} \text{ Solution}}$$ ■1S (*USP28*)

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Change to read:

Hydrochloric Acid, Normal (1 N)
HCl, **36.46**
36.46 g in 1000 mL

Dilute 85 mL of hydrochloric acid with water to 1000 mL. Standardize the solution as follows.

Accurately weigh about 5.0 g of tromethamine, previously dried at 105° for 3 hours. Dissolve in 50 mL of water, and add 2 drops of bromocresol green TS. Titrate with 1 N hydrochloric acid to a pale yellow endpoint. ~~Calculate the normality.~~

■ ■1S (*USP28*)
Each 121.14 mg of tromethamine is equivalent to 1 mL of 1 N hydrochloric acid.

$$\text{■N} = \frac{\text{mg tromethamine}}{121.14 \times \text{mL HCl}}\ \text{■1S (}USP28\text{)}$$

Add the following:

■Hydrochloric Acid, Half-Normal (0.5 N)

HCl, **36.46**

18.23 g in 1000 mL

To a 1000-mL volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add water to volume. Standardize the solution as follows.

Accurately weigh about 2.5 g of tromethamine, previously dried at 105° for 3 hours. Proceed as directed under *Hydrochloric Acid, Normal (1 N),* beginning with "Dissolve in 50 mL of water."

$$\text{N} = \frac{\text{mg tromethamine}}{121.14 \times \text{mL HCl}}\ \text{■1S (}USP28\text{)}$$

Change to read:

Hydrochloric Acid, Half-Normal (0.5 N) in Methanol
HCl, **36.46**
18.23 g in 1000 mL

To a 1000-mL volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add methanol to volume. Standardize the solution as follows.

Accurately weigh about 2.5 g of tromethamine, previously dried at 105° for 3 hours. Proceed as directed under *Hydrochloric Acid, Normal (1 N),* beginning with "Dissolve in 50 mL of water."

$$\text{■N} = \frac{\text{mg tromethamine}}{121.14 \times \text{mL HCl}}\ \text{■1S (}USP28\text{)}$$

Add the following:

■Hydrochloric Acid, Alcoholic, Tenth-Molar (0.1 M)

HCl, **36.46**

Dilute 9.0 mL with aldehyde free alcohol of hydrochloric acid to 1000 mL. ■1S (*USP28*)

Change to read:

Iodine, Tenth-Normal (0.1 N)
I, **126.90**
12.69 g in 1000 mL

Dissolve about 14 g of iodine in a solution of 36 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL, and standardize the solution as follows.

Transfer 25.0 mL of the iodine solution to a 250-mL flask, dilute with water to 100 mL, add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS and continue titrating until the solution is colorless. ~~Calculate the normality.~~

■ ■1S (*USP28*)
Preserve in amber-colored, glass-stoppered bottles.

$$\text{■N} = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{25}\ \text{■1S (}USP28\text{)}$$

Change to read:

■Iodine, Hundredth-Normal (0.01 N)
I, **126.90**
1.269 g in 1000 mL

Dissolve about 1.4 g of iodine in a solution of 3.6 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL, and standardize the solution as follows.

Transfer 100.0 mL of iodine solution to a 250-mL flask, add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS, and continue titrating until the solution is colorless. ~~Calculate the normality.~~

■■1S (*USP28*)
Preserve in amber-colored, glass-stoppered bottles.■1S (*USP28*)

$$N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{25}$$ ■1S (*USP28*)

Add the following:

■Lead Perchlorate, Tenth-Molar (0.1 M)

$Pb(ClO_4)_2 \cdot 3H_2O$, **460.15**

46.01 g in 1000 mL

Dissolve 46 g of lead perchlorate in water, and dilute with water to 1000.0 mL. Accurately weigh about 150 mg of sodium sulfate, previously dried at 105° for 4 hours, and dissolve in 50 mL of water. Add 50 mL of a mixture of water and formaldehyde (1 : 1), and stir for about 1 minute. Determine the endpoint potentiometrically using a lead ion selective electrode. Perform a blank determination, and make any necessary corrections. Each 14.204 mg of sodium sulfate is equivalent to 1 mL of 0.1 M lead perchlorate.

$$M = \frac{\text{mg sodium sulfate}}{142.04 \times \text{mL lead perchlorate}}$$ ■1S (*USP28*)

Change to read:

Lead Perchlorate, Hundredth-Molar (0.01 M)
$Pb(ClO_4)_2$ **406.10**

Accurately pipet 100 mL of commercially available 0.1 M lead perchlorate solution into a 1000-mL volumetric flask, add a sufficient quantity of water to make 1000 mL, and standardize the solution as follows.

Accurately pipet 50 mL of 0.01 M lead perchlorate solution, as prepared above, into a 250-mL conical flask. Add 3 mL of aqueous hexamethylenetetramine solution (2.0 g per 100 mL) and 4 drops of 0.5% xylenol orange indicator prepared by adding 500 mg of xylenol orange to 10 mL of alcohol and diluting with water to 100 mL. (Omit the alcohol if the sodium salt of the indicator is used). Titrate with 0.05 M edetate disodium VS to a yellow endpoint. ~~Calculate the molarity.~~

$$M = \frac{\text{mL edetate disodium} \times \text{M edetate disodium}}{50.0}$$ ■1S (*USP28*)

Change to read:

Lithium Methoxide, Fiftieth-Normal (0.02 N) in Methanol
CH_3LiO, **37.97**
759.6 mg in 1000 mL

Dissolve 0.12 g of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When the reaction is complete, add 850 mL of methanol, and mix. Store the solution preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under *Sodium Methoxide*, *Tenth-Normal* (*0.1 N*) (*in Toluene*), but use only 100 mg of benzoic acid. Each 2.442 mg of benzoic acid is equivalent to 1 mL of 0.02 N lithium methoxide.

NOTE—Restandardize the solution frequently.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL lithium methoxide (corrected for the blank)}}$$ ■1S (*USP28*)

Add the following:

▲Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol

CH_3OLi, **37.97**

3.798 g in 1000 mL

Dissolve 500 mg of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of methanol. If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under *Sodium Methoxide*, *Tenth-Normal* (*0.1 N*) (*in Toluene*).

NOTE—Restandardize the solution frequently.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL lithium methoxide (corrected for the blank)}}$$ ▲*USP 29*

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Change to read:

Lithium Methoxide, Tenth-Normal (0.1 N) in ~~Benzene~~

■**Toluene**■1S (*USP28*)
CH_3OLi, **37.97**
3.798 g in 1000 mL

Dissolve ~~0.6 g~~

■500 mg■1S (*USP28*)
of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of ~~benzene~~

■toluene■1S (*USP28*)
If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under *Sodium Methoxide*, *Tenth-Normal* (*0.1 N*) (*in Toluene*).

NOTE—Restandardize the solution frequently.

$$\blacksquare N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL lithium methoxide (corrected for the blank)}} \blacksquare 1S\ (USP28)$$

Change to read:

Mercuric Nitrate, Tenth-Molar (0.1 M)
$Hg(NO_3)_2$, **324.60**
32.46 g in 1000 mL

Dissolve about 35 g of mercuric nitrate in a mixture of 5 mL of nitric acid and 500 mL of water, and dilute with water to 1000 mL. Standardize the solution as follows.

Transfer an accurately measured volume of about 20 mL of the solution to a conical flask, and add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS. Cool to below 20°, and titrate with 0.1 N ammonium thiocyanate VS to the first appearance of a permanent brownish color. ~~Calculate the molarity.~~

$$\blacksquare M = \frac{\text{mL } NH_4SCN \times \text{N } NH_4SCN}{\text{mL } Hg(NO_3)_2} \blacksquare 1S\ (USP28)$$

Delete the following:

~~■**Morpholine, Half-Normal (0.5 N) in Methanol**~~
~~C_4H_9NO, **87.12**~~
~~43.56 g in 1000 mL~~

~~Transfer 44 mL of recently distilled morpholine to a 1-liter reagent bottle, and add methanol to make about 1 liter. Protect from absorption of carbon dioxide during withdrawal of aliquots. It is not necessary to standardize this solution.~~■1S (*USP28*)

Change to read:

Oxalic Acid, Tenth-Normal (0.1 N)
$H_2C_2O_4 \cdot 2H_2O$, **126.07**
6.303 g in 1000 mL

Dissolve 6.45 g of oxalic acid in water to make 1000 mL. Standardize by titration against freshly standardized 0.1 N potassium permanganate VS as directed under *Potassium Permanganate*, *Tenth-Normal* (*0.1 N*).

Preserve in glass-stoppered bottles, protected from light.

$$\blacksquare N = \frac{\text{mL } KMnO_4 \times \text{N } KMnO_4}{\text{mL } H_2C_2O_4} \blacksquare 1S\ (USP28)$$

Change to read:

Perchloric Acid, Tenth-Normal (0.1 N) (in Glacial Acetic Acid)
$HClO_4$, **100.46**
10.05 g in 1000 mL

NOTE—Where called for in the tests and assays, this volumetric solution is specified as "0.1 N perchloric acid." Thus, where 0.1 N or other strength of this volumetric solution is specified, the solution in glacial acetic acid is to be used, unless the words "in dioxane" are stated. [See also *Perchloric Acid, Tenth-Normal (0.1 N) in Dioxane*.]

Mix 8.5 mL of perchloric acid with 500 mL of glacial acetic acid and 21 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL. Alternatively, the solution may be prepared as follows. Mix 11 mL of 60 percent perchloric acid with 500 mL of glacial acetic acid and 30 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL.

Allow the prepared solution to stand for 1 day for the excess acetic anhydride to be combined, and determine the water content by *Method I* (see *Water Determination* ⟨921⟩), except to use a test specimen of about 5 g of the 0.1 N perchloric acid that is expected to contain approximately 1 mg of water and the *Reagent* (see *Reagent* under *Method Ia* in *Water Determination* ⟨921⟩) diluted such that 1 mL is equivalent to about 1 to 2 mg of water. If the water content exceeds 0.5%, add more acetic anhydride. If the solution contains no titratable water, add sufficient water to obtain a content of between 0.02% and 0.5% of water. Allow the solution to stand for 1 day, and again titrate the water content. The solution so obtained contains between 0.02% and 0.5% of water, indicating freedom from acetic anhydride.

Standardize the solution as follows.

Accurately weigh about 700 mg of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve it in 50 mL of glacial acetic acid in a 250-mL flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to blue-green. Deduct the volume of the perchloric acid consumed by 50 mL of the glacial acetic acid. ~~and calculate the normality.~~

■■1S (*USP28*)

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Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$\blacksquare N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL } HClO_4 \text{ solution (corrected for the blank)}} \blacksquare 1S\ (USP28)$$

Change to read:

Perchloric Acid, Tenth-Normal (0.1 N) in Dioxane

Mix 8.5 mL of perchloric acid with sufficient dioxane to make 1000 mL. Standardize the solution as follows.

Accurately weigh about 700 mg of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve in 50 mL of glacial acetic acid in a 250-mL flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to bluish green. ~~Deduct the volume of the perchloric acid consumed by 50 mL of the glacial acetic acid, and calculate the normality.~~

■Carry out a blank determination.■1S (*USP28*)

Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$\blacksquare N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL } HClO_4 \text{ solution (corrected for the blank)}} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Bromate, Tenth-Normal (0.1 N)
$KBrO_3$, **167.00**
2.784 g in 1000 mL

Dissolve 2.784 g of potassium bromate in water to make 1000 mL, and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a glass-stoppered flask, add 3 g of potassium iodide, and follow with 3 mL of hydrochloric acid. Allow to stand for 5 minutes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents, and calculate the normality.

$$\blacksquare N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{\text{mL } KBrO_3 \text{ Solution}} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Bromide-Bromate, Tenth-Normal (0.1 N)

Dissolve 2.78 g of potassium bromate ($KBrO_3$) and 12.0 g of potassium bromide (KBr) in water, and dilute with water to 1000 mL. Standardize by the procedure set forth for *Potassium Bromate, Tenth-Normal* (*0.1 N*).

$$\blacksquare N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{\text{mL } KBrO_3 / KBr} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Dichromate, Tenth-Normal (0.1 N)
$K_2Cr_2O_7$, **294.18**
4.903 g in 1000 mL

Dissolve about 5 g of potassium dichromate in 1000 mL of water. Standardize the solution as follows.

Transfer 25.0 mL of this solution to a glass-stoppered, 500-mL flask, add 2 g of potassium iodide (free from iodate), dilute with 200 mL of water, add 5 mL of hydrochloric acid, allow to stand for 10 minutes in a dark place, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. ~~Correct for a blank run on the same quantities of the same reagents, and calculate the normality.~~

■Carry out a blank determination.

$$N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{25.0} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Ferricyanide, Twentieth-Molar (0.05 M)
$K_3Fe(CN)_6$, **329.24**
16.46 g in 1000 mL

Dissolve about 17 g of potassium ferricyanide in water to make 1000 mL. Standardize the solution as follows.

Transfer 50.0 mL of this solution to a glass-stoppered, 500-mL flask, dilute with 50 mL of water, add 10 mL of potassium iodide TS and 10 mL of dilute hydrochloric acid, and allow to stand for 1

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minute. Then add 15 mL of zinc sulfate solution (1 in 10), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. ~~Calculate the molarity.~~

■■1S (*USP28*)
Protect from light, and restandardize before use.

$$\blacksquare M = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{50.0} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Hydroxide, Normal (1 N)
KOH, **56.11**
56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for *Sodium Hydroxide*, *Normal* (*1 N*).

$$\blacksquare N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH}} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Hydroxide, Alcoholic, Half-Normal (0.5 N)
28.06 g in 1000 mL

Dissolve about 34 g of potassium hydroxide in 20 mL of water, and add aldehyde-free alcohol to make 1000 mL. Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant into a suitable, tight container, and standardize the solution as follows.

Accurately measure about 25 mL of 0.5 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS, and titrate with the alcoholic potassium hydroxide solution until a permanent, pale pink color is produced. ~~Calculate the normality.~~

■■1S (*USP28*)

NOTE—Store in tightly stoppered bottles, protected from light.

$$\blacksquare N = \frac{\text{mL HCl} \times \text{N HCl}}{\text{mL KOH}} \blacksquare 1S\ (USP28)$$

Add the following:

■Potassium Hydroxide, Alcoholic, Tenth-Molar (0.1 M)

KOH, **56.11**

Dilute 20 mL of 0.5 M alcoholic potassium hydroxide with aldehyde-free alcohol to 100.0 mL.■1S (*USP28*)

Change to read:

Potassium Hydroxide, Methanolic, Tenth-Normal (0.1 N)
5.612 g in 1000 mL

Dissolve about 6.8 g of potassium hydroxide in 4 mL of water, and add methanol to make 1000 mL. Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant into a suitable, tight container, and standardize the solution as follows.

Measure accurately about 25 mL of 0.1 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS, and titrate with the methanolic potassium hydroxide solution until a permanent, pale pink color is produced. ~~Calculate the normality.~~

■■1S (*USP28*)
NOTE—Store in tightly stoppered bottles, protected from light.

$$\blacksquare N = \frac{\text{mL HCl} \times \text{N HCl}}{\text{mL KOH}} \blacksquare 1S\ (USP28)$$

Change to read:

Potassium Permanganate, Tenth-Normal (0.1 N)
$KMnO_4$, **158.03**
3.161 g in 1000 mL

Dissolve about 3.3 g of potassium permanganate in 1000 mL of water in a flask, and boil the solution for about 15 minutes. Insert the stopper in the flask, allow it to stand for at least 2 days, and filter through a fine-porosity, sintered-glass crucible. If necessary, the bottom of the sintered-glass crucible may be lined with a pledget of glass wool. Standardize the solution as follows.

Accurately weigh about 200 mg of sodium oxalate, previously dried at 110° to constant weight, and dissolve it in 250 mL of water. Add 7 mL of sulfuric acid, heat to about 70°, and then slowly add the permanganate solution from a buret, with constant stirring, until a pale pink color, which persists for 15 seconds, is produced. The temperature at the conclusion of the titration should be not less than 60°. Calculate the normality. Each ~~67.00 mg~~

■6.700 mg■1S (*USP28*)
of sodium oxalate is equivalent to 1 mL of 0.1 N potassium permanganate.

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Because potassium permanganate is reduced on contact with organic substances such as rubber, the solution must be handled in apparatus entirely of glass or other suitably inert material. It should be frequently restandardized. Store in glass-stoppered, amber-colored bottles.

$$\blacksquare N = \frac{\text{g } Na_2C_2O_4}{\text{mL } KMnO_4 \text{ solution} \times 0.06700} \blacksquare 1S\ (USP28)$$

Change to read:

Silver Nitrate, Tenth-Normal,(0.1 N)
$AgNO_3$, **169.87**
16.99 g in 1000 mL

Dissolve about 17.5 g of silver nitrate in 1000 mL of water, and standardize the solution as follows.

Transfer about 100 mg, accurately weighed, of reagent-grade sodium chloride, previously dried at 110° for 2 hours, to a 150-mL beaker, dissolve in 5 mL of water, and add 5 mL of acetic acid, 50 mL of methanol, and about 0.5 mL of eosin Y TS. Stir, preferably with a magnetic stirrer, and titrate with the silver nitrate solution. ~~Calculate the normality.~~

$$\blacksquare N = \frac{\text{mg NaCl}}{\text{mL } AgNO_3 \times 58.44} \blacksquare 1S\ (USP28)$$

Change to read:

Sodium Hydroxide, Normal (1 N)
NaOH, **40.00**
40.00 g in 1000 mL

Dissolve 162 g of sodium hydroxide in 150 mL of carbon dioxide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL.

Accurately weigh about 5 g of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each 204.2 mg of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$\blacksquare N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH solution}} \blacksquare 1S\ (USP28)$$

NOTES—(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., 0.1 N, 0.01 N) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon dioxide-free water to yield the desired concentration.

Restandardize the solution frequently.

Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)
NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% (w/w) solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced. ~~Calculate the normality as follows:~~

~~$W/122.12V$,~~

~~in which W is the weight, in mg, of benzoic acid taken, V is the volume, in mL, of alcoholic sodium hydroxide consumed, and 122.12 is the molecular weight of benzoic acid.~~

$$\blacksquare N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}} \blacksquare 1S\ (USP28)$$

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Change to read:

Sodium Methoxide, Tenth-Normal (0.1 N) (in Toluene)
CH_3ONa, **54.02**
5.402 g in 1000 mL

Cool in ice-water 150 mL of methanol contained in a 1000-mL volumetric flask, and add, in small portions, about 2.5 g of freshly cut sodium metal. When the metal has dissolved, add toluene to make 1000 mL, and mix. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution as follows.

Accurately weigh about 400 mg of primary standard benzoic acid, and dissolve in 80 mL of dimethylformamide in a flask. Add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with the sodium methoxide to a blue endpoint. Correct for the volume of the sodium methoxide solution consumed by 80 mL of the dimethylformamide. ~~and calculate the normality.~~

■■1S (*USP28*)
Each 12.21 mg of benzoic acid is equivalent to 1 mL of 0.1 N sodium methoxide.

$$\blacksquare N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium methoxide (corrected for the blank)}} \blacksquare 1S\ (USP28)$$

NOTES—(1) To eliminate any turbidity that may form following dilution with toluene, add methanol (25 to 30 mL usually suffices) until the solution is clear. (2) Restandardize the solution frequently.

Change to read:

Sodium Methoxide, Half-Normal (0.5 N) in Methanol
CH_3ONa, **54.02**
27.01 g in 1000 mL

Weigh 11.5 g of freshly cut sodium metal, and cut into small cubes. Place about 0.5 mL of anhydrous methanol in a round-bottom, 250-mL flask equipped with a ground-glass joint, add 1 cube of the sodium metal, and, when the reaction has ceased, add the remaining sodium metal to the flask. Connect a water-jacketed condenser to the flask, and slowly add 250 mL of anhydrous methanol, in small portions, through the top of the condenser. Regulate the addition of the methanol so that the vapors are condensed and do not escape through the top of the condenser. After addition of the methanol is complete, connect a drying tube to the top of the condenser, and allow the solution to cool. Transfer the solution to a 1-L volumetric flask, dilute with anhydrous methanol to volume, and mix. Standardize the solution as follows.

Accurately measure about 20 mL of freshly standardized 1 N hydrochloric acid VS into a 250-mL conical flask, add 0.25 mL of phenolphthalein TS, and titrate with the sodium methoxide solution to the first appearance of a permanent pink color. ~~Calculate the normality.~~

$$\blacksquare N = \frac{\text{mL HCl} \times \text{N HCl}}{\text{mL sodium methoxide}} \blacksquare 1S\ (USP28)$$

Change to read:

Sodium Nitrite, Tenth-Molar (0.1 M)
$NaNO_2$, **69.00**
6.900 g in 1000 mL

Dissolve 7.5 g of sodium nitrite in water to make 1000 mL, and standardize the solution as follows.

Accurately weigh about 500 mg of USP Sulfanilamide RS, previously dried at 105° for 3 hours, and transfer to a suitable beaker. Add 20 mL of hydrochloric acid and 50 mL of water, stir until dissolved, and cool to 15°. Maintaining the temperature at about 15°, titrate slowly with the sodium nitrite solution, placing the buret tip below the surface of the solution to preclude air oxidation of the sodium nitrite, and stir the solution gently with a magnetic stirrer, but avoid pulling a vortex of air beneath the surface. Use the indicator specified in the individual monograph, or, if a potentiometric procedure is specified, determine the endpoint electrometrically, using platinum-calomel or platinum-platinum electrodes. When the titration is within 1 mL of the endpoint, add the titrant in 0.1-mL portions, and allow 1 minute between additions. ~~Calculate the molarity.~~

■■1S (*USP28*)
Each 17.22 mg of sulfanilamide is equivalent to 1 mL of ~~1000 M~~

■0.1000 M■1S (*USP28*)
sodium nitrite.

$$\blacksquare M = \frac{\text{mg of sulfanilamide}}{172.22 \times \text{mL } NaNO_2} \blacksquare 1S\ (USP28)$$

Change to read:

Sodium Tetraphenylboron, Fiftieth-Molar (0.02 M)
$NaB(C_6H_5)_4$, **342.22**
6.845 g in 1000 mL

Dissolve an amount of sodium tetraphenylboron, equivalent to 6.845 g of $NaB(C_6H_5)_4$, in water to make 1000 mL, and standardize the solution as follows.

Pipet two 75-mL portions of the solution into separate beakers, and to each add 1 mL of acetic acid and 25 mL of water. To each beaker add, slowly and with constant stirring, 25 mL of potassium biphthalate solution (1 in 20), and allow to stand for 2 hours. Filter one of the mixtures through a filtering crucible, and wash the precipitate with cold water. Transfer the precipitate to a container, add 50 mL of water, shake intermittently for 30 minutes, filter, and use the filtrate as the saturated potassium tetraphenylborate solution in the following standardization procedure. Filter the second mixture through a tared filtering crucible, and wash the precipitate with three 5-mL portions of saturated potassium tetraphenylborate solution. Dry the precipitate at 105° for 1 hour. Each g of potassium tetraphenylborate is equivalent to 955.1 mg of sodium tetraphenylboron. ~~From the weight of sodium tetraphenylboron obtained, calculate the molarity of the sodium tetraphenylboron solution.~~

■■1S (*USP28*)
NOTE—Prepare this solution ~~fresh~~

■just before use.■1S (*USP28*)

In-Process Revision

Change to read:

Sodium Thiosulfate, Tenth-Normal (0.1 N)
$Na_2S_2O_3 \cdot 5H_2O$, **248.19**
24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried at 120° for 4 hours, and dissolve in 100 mL of water in a glass-stoppered, 500-mL flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the solution is yellowish-green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination. ~~Calculate the normality.~~

■■1S (*USP28*)
Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$■N = \frac{\text{mg } K_2Cr_2O_7}{49.04 \times \text{mL } Na_2S_2O_3}$$ ■1S (*USP28*)

Change to read:

Sulfuric Acid, Half-Normal (0.5 N) in Alcohol
H_2SO_4, **98.08**
24.52 g in 1000 mL

Add slowly, with stirring, 13.9 mL of sulfuric acid to a sufficient quantity of dehydrated alcohol to make 1000 mL. Cool, and standardize against tromethamine as described under *Hydrochloric Acid*, *Half-Normal* (*0.5 N*) *in Methanol.*

$$■N = \frac{\text{mg tromethamine}}{121.14 \times \text{mL } H_2SO_4}$$ ■1S (*USP28*)

Change to read:

Tetrabutylammonium Hydroxide, Tenth-Normal (0.1 N)
$(C_4H_9)_4NOH$, **259.47**
25.95 g in 1000 mL

Dissolve 40 g of tetra-*n*-butylammonium iodide in 90 mL of anhydrous methanol in a glass-stoppered flask. Place in an ice bath, add 20 g of powdered silver oxide, insert the stopper in the flask, and agitate vigorously for 60 minutes. Centrifuge a few mL, and test the supernatant for iodide (see *Iodide* ⟨191⟩). If the test is positive, add an additional 2 g of silver oxide, and continue to allow to stand for 30 minutes with intermittent agitation. When all of the iodide has reacted, pass through a fine-porosity, sintered-glass funnel. Rinse the flask and the funnel with three 50-mL portions of anhydrous toluene, adding the rinsings to the filtrate. Dilute with a mixture of three volumes of anhydrous toluene and 1 volume of anhydrous methanol to 1000 mL, and flush the solution for 10 minutes with dry, carbon dioxide-free nitrogen. [NOTE—If necessary to obtain a clear solution, further small quantities of anhydrous methanol may be added.] Store in a reservoir protected from carbon dioxide and moisture, and discard after 60 days. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available tetrabutylammonium hydroxide solution in methanol with a mixture of 4 volumes of anhydrous toluene and 1 volume of anhydrous methanol. [NOTE—If necessary to obtain a clear solution, further small quantities of methanol may be added.]

Standardize the solution on the day of use as follows. Dissolve about 400 mg of primary standard benzoic acid, accurately weighed, in 80 mL of dimethylformamide, add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate to a blue endpoint with the tetrabutylammonium hydroxide solution, delivering the titrant from a buret equipped with a carbon dioxide absorption trap. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N tetrabutylammonium hydroxide is equivalent to 12.21 mg of benzoic acid.

$$■N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL } (C_4H_9)_4NOH}$$ ■1S (*USP28*)

Change to read:

▲Tetrabutylammonium Hydroxide in Methanol/Isopropyl Alcohol, 0.1 N

Prepare as described for *Tetrabutylammonium Hydroxide, Tenth-Normal (0.1 N),* using isopropyl alcohol instead of toluene, and standardize as described. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available tetrabutylammonium hydroxide solution in methanol with 4 volumes of anhydrous isopropyl alcohol.

$$■N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL } (C_4H_9)_4NOH}$$ ■1S (*USP28*) ▲*USP28*

In-Process Revision

Change to read:

Tetramethylammonium Bromide, Tenth-Molar (0.1 M)
$(CH_3)_4NBr$, **154.05**
15.41 g in 1000 mL

Dissolve 15.41 g of tetramethylammonium bromide in water to make 1000 mL, and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a beaker, add 10 mL of diluted nitric acid and 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. ~~Calculate the molarity.~~

$$\blacksquare M = \frac{\text{mL } AgNO_3 \times \text{N } AgNO_3}{\text{mL } (CH_3)_4NBr} \quad \blacksquare 1S\ (USP28)$$

Change to read:

Tetramethylammonium Chloride, Tenth-Molar (0.1 M)
$(CH_3)_4NCl$, **109.60**
10.96 g in 1000 mL

Dissolve 10.96 g of tetramethylammonium chloride in water to make 1000 mL, and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a flask, add 10 mL of diluted nitric acid and 50.0 mL of 0.1 N silver nitrate VS, and mix. Add 5 mL of nitrobenzene and 2 mL of ferric ammonium sulfate TS, shake, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. ~~Calculate the molarity.~~

$$\blacksquare M = \frac{\text{mL } AgNO_3 \times \text{N } AgNO_3}{\text{mL } (CH_3)_4NCl} \quad \blacksquare 1S\ (USP28)$$

Change to read:

Titanium Trichloride, Tenth-Normal (0.1 N)
$TiCl_3$, **154.23**
15.42 g in 1000 mL

Add 75 mL of titanium trichloride solution (1 in 5) to 75 mL of hydrochloric acid, dilute to 1000 mL, and mix. Standardize the solution as follows, using the special titration apparatus described.

Apparatus—Store the titanium trichloride solution in the reservoir of a closed-system titration apparatus in an atmosphere of hydrogen.

Use a wide-mouth, 500-mL conical flask as the titration vessel, and connect it by means of a tight-fitting rubber stopper to the titration buret, an inlet tube for carbon dioxide, and an exit tube. Arrange for mechanical stirring. All joints must be airtight. Arrange to have both the hydrogen and the carbon dioxide pass through wash bottles containing titanium trichloride solution (approximately 1 in 50) to remove any oxygen.

If the solution to be titrated is to be heated before or during titration, connect the titration flask with an upright reflux condenser through the rubber stopper.

Standardization—Place an accurately measured volume of about 40 mL of 0.1 N ferric ammonium sulfate VS in the titration flask, and pass in a rapid stream of carbon dioxide until all the air has been removed. Add the titanium trichloride solution from the buret until near the calculated endpoint (about 35 mL), then add through the outlet tube 5 mL of ammonium thiocyanate TS, and continue the titration until the solution is colorless. ~~Calculate the normality.~~

$$\blacksquare N = \frac{\text{mL } FeNH_4(SO_4)_2 \times \text{N } FeNH_4(SO_4)_2}{\text{mL } TiCl_3} \quad \blacksquare 1S\ (USP28)$$

Change to read:

Zinc Sulfate, Twentieth-Molar (0.05 M)
$ZnSO_4 \cdot 7H_2O$, **287.56**
14.4 g in 1000 mL

Dissolve 14.4 g of zinc sulfate in water to make 1 L. Standardize the solution as follows.

Accurately measure about 10 mL of 0.05 M edetate disodium VS into a 125-mL conical flask, and add, in the order given, 10 mL of acetic acid-ammonium acetate buffer TS, 50 mL of alcohol, and 2 mL of dithizone TS. Titrate with the zinc sulfate solution to a clear, rose-pink color. ~~Calculate the molarity.~~

~~NOTE—For many of the reagents mentioned in the foregoing section, the corresponding standards of the 6th edition (1980) of *Reagent Chemicals*, published by the American Chemical Society, should be consulted. For a limited number of other reagents, the standards are adapted from those appearing in *Reagent Chemicals and Standards*, 5th edition, by Joseph Rosin and copyrighted by the publisher, D. Van Nostrand Co., Inc.~~

$$\blacksquare M = \frac{\text{mL edetate disodium} \times \text{M edetate disodium}}{\text{mL } ZnSO_4} \quad \blacksquare 1S\ (USP28)$$

In-Process Revision

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869 and page 2181 of *PF* 30(6) [Nov.–Dec. 2004].

(HDQ) RTS—41759-1; 41759-2

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:	
■Acetaminophen Tablets, Extended-Release	T■1S (*USP28*)
Add the following:	
■Benazepril Tablets	W■2S (*USP28*)
Add the following:	
■Bismuth Subsalicylate Tablets	T■2S (*USP28*)
Add the following:	
■Cefaclor Tablets	T■2S (*USP28*)
Add the following:	
■Chromium Picolinate Tablets	W■2S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Clarithromycin Tablets, Extended-Release	W■2S (*USP28*)
Add the following:	
■Black Cohosh Tablets	T, LR■2S (*USP28*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W■2S (*USP28*)
Add the following:	
■Diethylstilbestrol Diphosphate Tablets	W■2S (*USP28*)
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W■2S (*USP28*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W■2S (*USP28*)
Add the following:	
■Fluoxetine Capsules, Delayed-Release	T■1S (*USP28*)
Add the following:	
■Fosinopril Sodium Tablets	T■2S (*USP28*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T■2S (*USP28*)
Add the following:	
■Gabapentin Capsules	W■2S (*USP28*)

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Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Ginkgo Capsules	T, LR■2S (*USP28*)
Add the following:	
■Ginkgo Tablets	T, LR■2S (*USP28*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■■1S (*USP28*)
Add the following:	
■Indinavir Sulfate Capsules	T■2S (*USP28*)
Add the following:	
■Irbesartan Tablets	W■1S (*USP28*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP28*)
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S (*USP28*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■1S (*USP28*)
Add the following:	
■Lysine Hydrochloride Tablets	W■2S (*USP28*)
Add the following:	
■Metformin Hydrochloride Tablets	T■1S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Modafinil Tablets	T■2S (*USP28*)
Add the following:	
■Naproxen Tablets, Delayed-Release	W■1S (*USP28*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■2S (*USP28*)
Add the following:	
■Oxaprozin Tablets	T, LR■2S (*USP28*)
Add the following:	
■Pygeum Capsules	T■1S (*USP28*)
Add the following:	
■Quinapril Tablets	W■2S (*USP28*)
Add the following:	
■Stavudine Capsules	T■1S (*USP28*)
Add the following:	
■Tolcapone Tablets	T■1S (*USP28*)
Add the following:	
■Valerian Capsules	T, LR■1S (*USP28*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■2S (*USP28*)
Add the following:	
▲Zinc Sulfate Tablets	W▲(*USP29*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 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 812 of *PF* 29(3) [May–June 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 2057 of *PF* 29(6) [Nov.–Dec. 2003], page 1050 of *PF* 30(3) [May–June 2004], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], and page 2183 of *PF* 30(6) [Nov.–Dec. 2004].

(HDQ) RTS—41206-1; 41637-1; 41689-1; 41731-1; 41731-2; 41731-3

Add the following:

▲**Meloxicam:** Pale yellow powder. Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in methanol and in alcohol; practically insoluble in water.▲*USP29*

Add the following:

▲**Tiamulin:** A sticky, translucent yellowish mass, slightly hygroscopic. Very soluble in dichloromethane; freely soluble in dehydrated alcohol; practically insoluble in water.▲*USP29*

In-Process Revision

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

Tests and Assays—See PF Vol. 30 No. 3, page 795.
Preservation, Packaging, Storage, and Labeling—See PF Vol. 30 No. 5, page 1574.

USP MONOGRAPHS

Acepromazine Maleate—See PF Vol. 29 No. 6, page 1832.
Acepromazine Maleate Injection—See PF Vol. 30 No. 4, page 1161.
Acetaminophen Extended-Release Tablets—See PF Vol. 30 No. 4, page 1161.
Acetaminophen Oral Suspension—See PF Vol. 30 No. 5, page 1579.
Acetaminophen and Aspirin Tablets—See PF Vol. 30 No. 1, page 41.
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 30 No. 1, page 43.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—See PF Vol. 30 No. 1, page 42.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 30 No. 1, page 44.
Acetaminophen and Codeine Phosphate Capsules—See PF Vol. 30 No. 1, page 45.
Acetaminophen and Diphenhydramine Citrate Tablets—See PF Vol. 30 No. 1, page 47.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 30 No. 1, page 47.
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 30 No. 1, page 48.
Acetohydroxamic Acid—See PF Vol. 30 No. 5, page 1579.
Acetohydroxamic Acid Tablets—See PF Vol. 30 No. 1, page 49.
Acyclovir—See PF Vol. 30 No. 5, page 1580.
Adenosine—See PF Vol. 29 No. 6, page 1834.
Medical Air—See PF Vol. 28 No. 4, page 1065.
Albendazole Oral Suspension—See PF Vol. 30 No. 4, page 1163.
Albumin Human—See PF Vol. 29 No. 4, page 992.
Albuterol Tablets—See PF Vol. 30 No. 1, page 50.
Alcohol in Dextrose Injection—See PF Vol. 30 No. 5, page 1581.
Alendronate Sodium Tablets—See PF Vol. 28 No. 3, page 740.
Alfentanil Hydrochloride—See PF Vol. 29 No. 6, page 1834.
Allopurinol—See PF Vol. 28 No. 5, page 1386.
Alprazolam Tablets—See PF Vol. 30 No. 5, page 1582.
Alprostadil—See PF Vol. 29 No. 5, page 1412.
Alteplase—See PF Vol. 29 No. 6, page 1835.
Altretamine—See PF Vol. 27 No. 3, page 2514.
Alumina, Magnesia, and Calcium Carbonate Tablets—See PF Vol. 29 No. 6, page 1835.
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets—See PF Vol. 29 No. 6, page 1836.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets—See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, and Simethicone Tablets—See PF Vol. 29 No. 6, page 1841.
Alumina, Magnesia, and Simethicone Chewable Tablets—See PF Vol. 29 No. 6, page 1842.
Amantadine Hydrochloride Capsules—See PF Vol. 30 No. 1, page 51.
Amifostine—See PF Vol. 30 No. 6, page 1974.
Amifostine for Injection—See PF Vol. 30 No. 6, page 1976.
Aminocaproic Acid—See PF Vol. 29 No. 5, page 1414.
Aminopentamide Sulfate—See PF Vol. 30 No. 4, page 1163.
Aminophylline—See PF Vol. 29 No. 5, page 1414.
Aminosalicylate Sodium Tablets—See PF Vol. 30 No. 1, page 53.
Amitriptyline Hydrochloride—See PF Vol. 29 No. 6, page 1844.
Ammonium Chloride—See PF Vol. 29 No. 5, page 1415.
Ammonium Molybdate—See PF Vol. 29 No. 5, page 1416.
Amoxicillin Capsules—See PF Vol. 30 No. 5, page 1583.
Amoxicillin Tablets—See PF Vol. 30 No. 6, page 1977.
Amphetamine Sulfate—See PF Vol. 30 No. 3, page 807.
Amphetamine Sulfate Tablets—See PF Vol. 30 No. 1, page 54.
Amphotericin B Lotion—See PF Vol. 30 No. 2, page 444.
Amphotericin B Topical Emulsion—See PF Vol. 30 No. 2, page 445.
Ampicillin—See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules—See PF Vol. 30 No. 1, page 55.
Ampicillin Tablets—See PF Vol. 30 No. 1, page 56.
Anecortave Acetate—See PF Vol. 30 No. 2, page 445.
Anecortave Acetate Injectable Suspension—See PF Vol. 30 No. 2, page 447.
Anileridine—See PF Vol. 29 No. 6, page 1846.
Anticoagulant Citrate Dextrose Solution—See PF Vol. 30 No. 5, page 1583.
Ascorbic Acid Tablets—See PF Vol. 30 No. 1, page 60.
L-Asparagine—See PF Vol. 29 No. 3, page 687.
Aspartic Acid—See PF Vol. 30 No. 4, page 1163.
Aspirin—See PF Vol. 30 No. 4, page 1164.
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—See PF Vol. 30 No. 1, page 60.
Atenolol—See PF Vol. 29 No. 5, page 1416.
Atenolol Tablets—See PF Vol. 29 No. 1, page 49.
Atracurium Besylate—See PF Vol. 29 No. 6, page 1846.
Atracurium Besylate Injection—See PF Vol. 30 No. 3, page 808.
Atropine Sulfate—See PF Vol. 29 No. 6, page 1847.
Aurothioglucose—See PF Vol. 29 No. 6, page 1847.
Avobenzone—See PF Vol. 30 No. 4, page 1164.
Azaperone—See PF Vol. 29 No. 6, page 1847.
Baclofen Tablets—See PF Vol. 30 No. 1, page 61.
Benazepril Hydrochloride—See PF Vol. 29 No. 5, page 1422.
Benazepril Hydrochloride Tablets—See PF Vol. 29 No. 3, page 606.
Benzocaine—See PF Vol. 30 No. 3, page 809.
Benzoyl Peroxide Gel—See PF Vol. 30 No. 4, page 1165.
Benzoyl Peroxide Lotion—See PF Vol. 30 No. 2, page 456.
Benzoyl Peroxide Topical Emulsion—See PF Vol. 30 No. 2, page 456.
Benztropine Mesylate—See PF Vol. 29 No. 6, page 1848.
Benzyl Benzoate Lotion—See PF Vol. 30 No. 2, page 457.
Benzyl Benzoate Topical Emulsion—See PF Vol. 30 No. 2, page 457.
Betahistine Hydrochloride—See PF Vol. 30 No. 5, page 1584.
Betamethasone Tablets—See PF Vol. 30 No. 1, page 62.
Betamethasone Dipropionate Lotion—See PF Vol. 30 No. 2, page 458.
Betamethasone Dipropionate Topical Emulsion—See PF Vol. 30 No. 2, page 459.
Betamethasone Sodium Phosphate—See PF Vol. 30 No. 4, page 1166.
Betamethasone Valerate Lotion—See PF Vol. 30 No. 2, page 461.
Betamethasone Valerate Topical Emulsion—See PF Vol. 30 No. 2, page 461.
Bethanechol Chloride—See PF Vol. 30 No. 5, page 1586.
Bethanechol Chloride Tablets—See PF Vol. 30 No. 5, page 1587.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers—See PF Vol. 30 No. 1, page 63.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions—See PF Vol. 30 No. 1, page 66.
Biperiden—See PF Vol. 29 No. 6, page 1851.

Bismuth Subsalicylate Oral Suspension—See PF Vol. 30 No. 4, page 1166.
Bismuth Subsalicylate Tablets—See PF Vol. 30 No. 4, page 1167.
Bisoprolol Fumarate Tablets—See PF Vol. 30 No. 5, page 1588.
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Tetramethylammonium Chloride, Tenth-Molar (0.1 M)—See PF Vol. 30 No. 4, page 1403.
Titanium Trichloride, Tenth-Normal (0.1 N)—See PF Vol. 30 No. 4, page 1403.
Zinc Sulfate, Twentieth-Molar (0.05 M)—See PF Vol. 30 No. 4, page 1403.

Reagent Footnotes

Reagent Footnotes—See PF Vol. 30 No. 2, pages 647–648.
Footnote 112—See PF Vol. 30 No. 1, page 317.
Footnote 113—See PF Vol. 30 No. 2, page 648.
Footnote 114—See PF Vol. 30 No. 2, page 648.
Footnote 115—See PF Vol. 30 No. 2, page 648.
Footnote 116—See PF Vol. 30 No. 2, page 648.

REFERENCE TABLES

Container Specifications for Capsules and Tablets—See 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. 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; PF Vol. 29 No. 5, page 1683; PF Vol. 29 No. 6, page 2055; PF Vol. 30 No. 2, page 648; PF Vol. 30 No. 3, page 1048; PF Vol. 30 No. 4, page 1404.
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. 4, page 8589; PF Vol. 25 No. 5, page 8917; PF Vol. 25 No. 6, page 9254; 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. 6, page 3374; PF Vol. 28 No. 2, page 554; 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; PF Vol. 29 No. 5, page 1684; PF Vol. 29 No. 6, page 2057; PF Vol. 30 No. 1, page 317; PF Vol 30 No. 2, page 650; PF Vol. 30 No. 3, page 1050; PF Vol. 30 No. 4, page 1405.

EXCIPIENTS

Excipients, USP and NF Excipients, Listed by Category—See PF Vol. 29 No. 4, page 1088; PF Vol. 29 No. 6, page 2008; PF Vol. 30 No. 2, page 587; PF Vol 30 No. 3, page 961; PF Vol. 30 No. 4, page 1317.

GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 28 No. 1, page 88.

NF MONOGRAPHS

Acesulfame Potassium—See PF Vol. 30 No. 2, page 591.
Adipic Acid—See PF Vol. 30 No. 4, page 1322.
Alfadex—See PF Vol. 30 No. 1, page 202.
Ammonium Sulfate—See PF Vol. 30 No. 3, page 966.
L-Asparagine—See PF Vol. 30 No. 1, page 205.
Aspartame Acesulfame—See PF Vol. 29 No. 2, page 453.
Betadex—See PF Vol. 30 No. 4, page 1323.
Butylparaben—See PF Vol. 29 No. 5, page 1598.
Calcium Silicate—See PF Vol. 30 No. 2, page 595.
Candelilla Wax—See PF Vol. 30 No. 3, page 966.
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Carbomer 940—See PF Vol. 30 No. 4, page 1328.
Carbomer Homopolymer—See PF Vol. 29 No. 6, page 2013.
Carboxymethylcellulose Calcium—See PF Vol. 23 No. 6, page 5063.
Low-Substituted Carboxymethylcellulose Sodium—See PF Vol. 30 No. 3, page 966.
Carboxymethylcellulose Sodium Suspension—See PF Vol. 25 No. 3, page 8088.
Cellaburate—See PF Vol. 30 No. 3, page 967.
Cetrimonium Bromide—See PF Vol. 30 No. 3, page 970.
Cetyl Alcohol—See PF Vol. 30 No. 3, page 970.
Cocoa Butter—See PF Vol. 30 No. 1, page 207.
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Croscarmellose Sodium—See PF Vol. 23 No. 3, page 4007.
Crospovidone—See PF Vol. 24 No. 1, page 5482.
Dibutyl Phthalate—See PF Vol. 30 No. 3, page 974.
Diethylene Glycol Stearates—See PF Vol. 30 No. 3, page 974.
Dimethicone—See PF Vol. 29 No. 1, page 142.
Ethylene Glycol Stearates—See PF Vol. 30 No. 3, page 974.
Ethylparaben—See PF Vol. 29 No. 5, page 1599.
Galactose—See PF Vol. 30 No. 2, page 600.
Gellan Gum—See PF Vol. 30 No. 4, page 1328.
Glyceryl Distearate—See PF Vol. 30 No. 3, page 975.
Glyceryl Monolinoleate—See PF Vol. 30 No. 3, page 975.
Glyceryl Monooleate—See PF Vol. 30 No. 3, page 975.
Glyceryl Monostearate—See PF Vol. 30 No. 3, page 975.
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Hymetellose—See PF Vol. 30 No. 3, page 975.
Hypromellose Acetate Succinate—See PF Vol. 30 No. 3, page 976.
Hypromellose Phthalate—See PF Vol. 30 No. 3, page 984.
Lauroyl Macrogolglycerides—See PF Vol. 26 No. 2, page 456.
Linoleoyl Polyoxylglycerides—See PF Vol. 30 No. 4, page 1328.
Magnesium Stearate—See PF Vol. 29 No. 6, page 2018.
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Maltitol Solution—See PF Vol. 30 No. 3, page 984.
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Maltose—See PF Vol. 30 No. 3, page 985.
Methylparaben—See PF Vol. 29 No. 5 page 1599.
Mono- and Di-glycerides—See PF Vol. 30 No. 4, page 1330.
Nitrogen—See PF Vol. 30 No. 2, page 604.
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Oleoyl Polyoxylglycerides—See PF Vol. 30 No. 4, page 1330.
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Sodium Stearyl Fumarate—See PF Vol. 30 No. 2, page 609.
Sodium Sulfite—See PF Vol. 30 No. 2, page 609.
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Sorbitol—See PF Vol. 30 No. 3, page 992.
Anhydrized Liquid Sorbitol—See PF Vol. 30 No. 3, page 993.
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Noncrystallizing Sorbitol Solution—See PF Vol. 30 No. 3, page 995.
Hydrogenated Soybean Oil—See PF Vol. 30 No. 3, page 995.
Modified Starch—See PF Vol. 30 No. 4, page 1334.
Pregelatinized Starch—See PF Vol. 30 No. 3, page 997.
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Stearic Acid—See PF Vol. 29 No. 2, page 480.
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Stearoyl Polyoxylglycerides—See PF Vol. 30 No. 4, page 1336.
Succinic Acid—See PF Vol. 30 No. 2, page 612.
Sunflower Oil—See PF Vol. 27 No. 4, page 2803.
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.
Medium-Chain Triglycerides—See PF Vol. 30 No. 3, page 998.

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* 31(1)–*PF* 31(6)]

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†Albendazole Oral Suspension—*Labeling*	29	4	991
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†1,1,4,4-Tetraphenyl-1,3-butadiene (added)	26	6	1623
†Trioleoylglycerol (added)—*Preview*	26	6	1623
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†Adipic Acid—*Packaging and storage*	30	4	1322
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†New cancellations in *PF* 31(1).

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

Aspirin Delayed-Release Capsules, *USP 28* page 182. It is proposed to revise references to the General Chapter *Drug Release* ⟨724⟩, which will affect monographs where the procedure or acceptance criteria are now to refer to the harmonized text of *Dissolution* ⟨711⟩. These proposed changes are being published in this issue of *PF* for information only, not for public comment, and are scheduled for publication in the *Second Interim Revision Announcement to USP 28–NF 23* with a scheduled delayed implementation date of **April 1, 2006**. Earlier implementation by individual companies may be done at their discretion.

Other monographs affected by this decision are the following:

Aspirin Delayed-Release Tablets
Aspirin Extended-Release Tablets
Bupropion Hydrochloride Extended-Release Tablets
Carbamazepine Extended-Release Tablets
Carbamazepine Tablets
Cefaclor Extended-Release Tablets
Chlorpheniramine Maleate Extended-Release Capsules
Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Capsules
Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Tablets
Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-Release Capsules
Clonidine Transdermal System
Conjugated Estrogens Tablets
Diazepam Extended-Release Capsules
Diclofenac Sodium Delayed-Release Tablets
Diltiazem Hydrochloride Extended-Release Capsules
Dirithromycin Delayed-Release Tablets
Disopyramide Phosphate Extended-Release Capsules
Divalproex Sodium Delayed-Release Tablets
Doxycycline Hyclate Delayed-Release Capsules
Erythromycin Delayed-Release Capsules
Erythromycin Delayed-Release Tablets
Felodipine Extended-Release Tablets
Ferrous Fumarate and Docusate Sodium Extended-Release Tablets
Garlic Delayed-Release Tablets
Hydroxyzine Hydrochloride Tablets
Indomethacin Extended-Release Capsules
Isosorbide Dinitrate Extended-Release Capsules
Isosorbide Dinitrate Extended-Release Tablets
Lansoprazole Delayed-Release Capsules
Liothyronine Sodium Tablets
Lithium Carbonate Extended-Release Tablets
Mesalamine Delayed-Release Tablets
Mesalamine Extended-Release Capsules
Methylphenidate Hydrochloride Extended-Release Tablets
Metoprolol Succinate Extended-Release Tablets
Morphine Sulfate Extended-Release Capsules
Nicotine Transdermal System
Nifedipine Extended-Release Tablets
Nitrofurantoin Capsules
Omeprazole Delayed-Release Capsules
Oxprenolol Hydrochloride Extended-Release Tablets
Oxtriphylline Extended-Release Tablets
Pentoxifylline Extended-Release Tablets
Phenylpropanolamine Hydrochloride Extended-Release Capsules
Phenylpropanolamine Hydrochloride Extended-Release Tablets
Pilocarpine Ocular System
Procainamide Hydrochloride Extended-Release Tablets
Progesterone Intrauterine Contraceptive System
Propranolol Hydrochloride Extended-Release Capsules
Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules
Pseudoephedrine Hydrochloride Extended-Release Capsules
Pseudoephedrine Hydrochloride Extended-Release Tablets
Quinidine Gluconate Extended-Release Tablets
Quinidine Sulfate Extended-Release Tablets
Sulfasalazine Delayed-Release Tablets
Theophylline Extended-Release Capsules
Trihexyphenidyl Hydrochloride Extended-Release Capsules
Verapamil Hydrochloride Extended-Release Tablets

(BPC: W. Brown) RTS—42035-18

Change to read:

~~**Drug release,** *Method A* ⟨724⟩~~—

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method A* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•²

Apparatus 1: 100 rpm.

Time: 90 minutes, for *Buffer stage*.

Diluent—Prepare a mixture of 0.1 N hydrochloric acid and 0.20 M tribasic sodium phosphate (3 : 1), and adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Procedure—Determine the amount of $C_9H_8O_4$ dissolved by determining UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid (about 280 nm in the *Acid stage*, and about 265 nm in the *Buffer stage*) using a filtered portion of the solution under test, diluted, if necessary, with 0.1 N hydrochloric acid (analyzing the *Acid stage*) and with *Diluent* (analyzing the *Buffer stage*), in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same medium.

•(Official April 1, 2006)•²

Harmonization

BRIEFING

Aspirin Delayed-Release Tablets, *USP 28* page 184—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-19

Change to read:

~~**Drug release,** *Method B* ⟨724⟩—~~

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2
Apparatus 1: 100 rpm.
Time: 90 minutes, for *Buffer stage*.
Diluent—Prepare a mixture of 0.1 N hydrochloric acid and 0.20 M tribasic sodium phosphate (3 : 1), and adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved by determining UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid (about 280 nm in the *Acid stage*, and about 265 nm in the *Buffer stage*) using a filtered portion of the solution under test, diluted, if necessary, with 0.1 N hydrochloric acid (analyzing the *Acid stage*) and with *Diluent* (analyzing the *Buffer stage*), in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same medium.

•(Official April 1, 2006)•2

BRIEFING

Aspirin Extended-Release Tablets, *USP 28* page 185—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-20

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 60 rpm.
Times: 1 hour and 4 hours.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved from UV absorbances at the isosbestic point at about 280 nm, using filtered portions of the solution under test, suitably diluted with 0.1 N hydrochloric acid, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same medium.
Tolerances—The percentages of the labeled amount of $C_9H_8O_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 20% and 55%
4	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2
Medium: water; 1000 mL.
Apparatus 2: 30 rpm.
Times: 1, 2, 4, and 8 hours.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved from UV absorbances at the isosbestic point at about 265 nm, using filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same medium. [NOTE—Prepare the Standard solution at the time of use. An amount of alcohol not to exceed 5% of the total volume of the Standard solution may be used to bring the Reference Standard into solution prior to dilution with *Medium*.]
Tolerances—The percentages of the labeled amount of $C_9H_8O_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 15% and 40%
2	between 25% and 60%
4	between 35% and 75%
8	not less than 70%

•(Official April 1, 2006)•2

BRIEFING

Bupropion Hydrochloride Extended-Release Tablets, *USP 28* page 297 and page 1562 of the *Fifth Interim Revision Announcement to USP 27–NF22*—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-45

Change to read:

Labeling—When more than one ~~*Drug Release* test~~

•*Dissolution Test*•2
is given, the labeling states the ~~*Drug Release test*~~

•*Dissolution Test*•2
used only if *Test 1* is not used.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

•TEST 1—•5
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 1, 4, and 8 hours.
Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* ⟨724⟩~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

•TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug release Test 2.*~~

•USP *Dissolution Test 2.*•2
Medium: 0.1 N hydrochloric acid, pH 1.5; 900 mL.
Apparatus 1: 50 rpm.
Times: 1, 2, 4, and 6 hours.
Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.
Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*
Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains 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 column efficiency is not less than 2000 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* ⟨724⟩~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug release Test 3.*~~

•USP *Dissolution Test 3.*•2
Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except using the wavelength of about 250 nm.
Times: 1, 2, 4, and 6 hours.
Tolerances: The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* ⟨724⟩~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

•5

•(Official April 1, 2006)•2

Harmonization

BRIEFING

Carbamazepine Tablets, *USP 28* page 342—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-46

Change to read:

Dissolution ⟨711⟩—

FOR PRODUCTS LABELED AS 100-MG CHEWABLE TABLETS:

TEST 1— If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: water containing 1% sodium lauryl sulfate; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 288 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium.* [NOTE—A volume of methanol not exceeding 1% of the final total volume of the Standard solution may be used to dissolve the carbamazepine.]

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use ~~the *Acceptance Table* under *Dissolution* ⟨711⟩;~~

•*Acceptance Table 1,*•2
with the following exceptions: at S_2, no unit is less than Q – 5%; at S_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

TEST 4— If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: 0.1 N hydrochloric acid containing 1% sodium lauryl sulfate; 225 mL. Add 2 drops of simethicone to each.

Apparatus 3: ~~(see *Drug release* ⟨724⟩.)~~

••2
35 dips per minute; use 20-mesh screen on the top of the reciprocating cylinder and a 100-mesh screen on the bottom of the reciprocating cylinder.

Time: 60 minutes.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes, the acceptance criteria specified for *Test 1* being used.

FOR PRODUCTS LABELED AS 200-MG TABLETS:

TEST 2— If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances*—Between 45% and 75% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩;~~

•*Acceptance Table 2,*•2
with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

TEST 3— If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances*—Between 60% and 85% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩;~~

•*Acceptance Table 2,*•2
with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

•(Official April 1, 2006)•2

BRIEFING

Carbamazepine Extended-Release Tablets, *USP 28* page 343—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-47

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
Medium: water; 900 mL, 1800 mL for 400-mg Tablets.

Apparatus 1: 100 rpm.

Times: 3, 6, 12, and 24 hours.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.

Tolerances—The percentages *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 10% and 35%
6	between 35% and 65%
12	between 65% and 90%
24	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Cefaclor Extended-Release Tablets, *USP 28* page 371—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-48

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1 (10-mesh basket): 100 rpm.
Times: 30, 60, and 240 minutes.
Procedure—Dilute filtered portions of the solution under test quantitatively with 0.1 N hydrochloric acid to obtain a test solution having a concentration of cefaclor ($C_{15}H_{14}ClN_3O_4S$) estimated to be about 25 µg per mL. Determine the amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 265 nm, in comparison with a Standard solution having a similar, known concentration of USP Cefaclor RS in the same *Medium*.
Tolerances—The percentages of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$) dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (minutes)	Amount dissolved
30	between 5% and 30%
60	between 20% and 50%
240	not less than 80%

•(Official April 1, 2006)•2

BRIEFING

Chlorpheniramine Maleate Extended-Release Capsules, *USP 28* page 448—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-49

Change to read:

Labeling—Label the Capsules to indicate the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
TEST 1— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: water; 500 mL.
Apparatus 1: 100 rpm.
Times: 1.5, 6.0, and 10.0 hours.
Procedure—Determine the amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved employing the method set forth in the *Assay*, using a filtered portion of the solution under test in comparison with a Standard solution having a known concentration of USP Chlorpheniramine Maleate RS in the same medium.
Tolerances—The percentages of the labeled amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1.5	between 15% and 40%
6.0	between 50% and 80%
10.0	not less than 70%

TEST 2— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2
Proceed as directed for *Procedure* ~~for *Delayed-Release (Enteric-Coated) Articles—General Drug Release Standard.*~~

•for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2
Medium—Prepare as directed under *Method B,* except use 900 mL of media. Operate the apparatus for 1 hour in the *Acid Stage* and use the acceptance criteria given under *Tolerances*. Operate the apparatus for 6 hours in the *Buffer Stage*, except to use 900 mL of simulated intestinal fluid TS without enzyme, and use the acceptance criteria given under *Tolerances*.
Apparatus 2: 50 rpm.

Times: 1.0 hour, 3.0 hours, 7.0 hours.
Procedure—Proceed as directed in *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1.0	between 30% and 60%
3.0	between 55% and 85%
7.0	not less than 70%

•(Official April 1, 2006)•2

BRIEFING

Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Capsules, *USP 28* page 451—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-50

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•2
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for phenylpropanolamine hydrochloride.*
Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved at the specified times conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Tablets, *USP 28* page 451—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-51

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•2
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for phenylpropanolamine hydrochloride.*
Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved at the specified times conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-Release Capsules, *USP 28* page 452—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-1

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•₂

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•₂

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 3, 6, and 12 hours.

Procedure—Determine the amounts of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for pseudoephedrine hydrochloride*, respectively.

Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_{10}H_{15}NO \cdot HCl$ dissolved at the specified times conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•₂

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

TEST 2— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•₂

Medium 1: simulated gastric fluid TS, prepared without pepsin; 900 mL.

Medium 2: simulated intestinal fluid TS, prepared without pancreatin; 900 mL.

Apparatus 2: 50 rpm.

Time for Medium 1: 1.5 hours.

Times for Medium 2: 3 and 6 hours.

Procedure—Determine the amounts of chlorpheniramine maleate ($C_{16}N_{19}ClN_2 \cdot C_4H_4O_4$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for pseudoephedrine hydrochloride*, respectively, using Standard solutions having known concentrations of the relevant USP Reference Standard in the appropriate *Medium.*

Tolerances—The percentages of the labeled amounts of $C_{16}N_{19}ClN_2 \cdot C_4H_4O_4$ and $C_{10}H_{15}NO \cdot HCl$ dissolved at the specified times conform to ~~*Acceptance Table 2.*~~

•*Acceptance Table 2.*•₂

Time (hours)	Amount dissolved (*Medium 1*)	Amount dissolved (*Medium 2*)
1.5	between 15% and 40%	
3.0		between 35% and 75%
6.0		not less than 50%

•(Official April 1, 2006)•₂

BRIEFING

Clonidine Transdermal System, *USP 28* page 515—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-53

Change to read:

Drug release ⟨724⟩—

Medium: 0.001 M phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; 200 mL for systems containing more than 5 mg of clonidine.

Times: 8, 24, 96, and 168 hours.

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 inches, 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 immersion. 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.

Mobile phase—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⟩).

System suitability solution—Prepare a solution of USP Clonidine 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 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 the 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 220-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 *System suitability solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the capacity factor is not less

* 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.

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 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, in 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 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.*~~

•*Acceptance Table 1* under *Drug Release* ⟨724⟩.•₂

Time (hours)	Time for sampling (hours)	Release rate (µg/h/cm^2)
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

•(Official April 1, 2006)•₂

BRIEFING

Diazepam Extended-Release Capsules, *USP 28* page 619—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-54

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•₂

Medium: simulated gastric fluid TS, prepared without enzymes; 900 mL.

Apparatus 1: 100 rpm.

Times: 1 hour; 4 hours; 8 hours; 12 hours.

Mobile phase—Prepare a suitable degassed and filtered mixture of methanol and water (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Buffer solution—Dissolve 77.1 g of ammonium acetate in water to make 1000 mL of solution, and adjust with ammonium hydroxide to a pH of 8.7.

Standard solution—Dissolve an accurately weighed quantity of USP Diazepam RS in *Medium*, dilute quantitatively with *Medium* to obtain a solution having a known concentration of about 0.15 mg per mL, and mix. Transfer 2.0-, 5.0-, 8.0-, and 10.0-mL aliquots of this solution to separate 100-mL volumetric flasks, add *Medium* to volume, and mix. Pipet 1.0 mL of each solution and 1.0 mL of *Buffer solution* into individual small vials, mix, and allow to stand at room temperature for about 10 minutes.

Test solution—Wrap each Capsule in a coil made from a 10-cm piece of 18-gauge copper wire weighing approximately 750 mg, so that the wire encircles the Capsule 4 times. The Capsule enclosed in the coil remains at the bottom of the basket (it should not float). Filter a portion of the solution under test, obtained at each time interval, through a suitable 0.6-µm porosity filter. Pipet 1.0 mL of each solution and 1.0 mL of *Buffer solution* into individual small vials, mix, and allow to stand at room temperature for about 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and an 8-mm × 10-cm column that contains packing L1. The flow rate is about 5.0 mL per minute. Chromatograph the appropriate *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not greater than 1.7; 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of $C_{16}H_{13}ClN_2O$ dissolved from peak responses of diazepam obtained from the *Test solution* and the *Standard solution*.

Tolerances—The percentage of the labeled amount of $C_{16}H_{13}ClN_2O$ dissolved is within the range stated at each of the following times.

Time (hours)	Amount dissolved
1	between 15% and 27%
4	between 49% and 66%
8	between 76% and 96%
12	between 85% and 115%

•(Official April 1, 2006)•₂

BRIEFING

Diclofenac Sodium Delayed-Release Tablets, *USP 28* page 626 and page 1986 of *PF* 30(6) [Nov.–Dec. 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-55

Change to read:

~~**Drug release,** *Method B* ⟨724⟩~~

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2 (paddles constructed of, or coated with, polytef being used): 50 rpm.

Procedure—At the end of 2 hours, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the *Buffer stage*. To the 0.1 N hydrochloric acid remaining in each vessel, add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer ~~2.0 mL~~

■3.0 mL■2S (*USP28*)

of this solution to a second 100-mL volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900 : 20) to volume, and mix. This Standard solution contains about 13.6 µg of USP Diclofenac Sodium RS per mL.

BUFFER STAGE—

pH 6.8 Phosphate buffer—Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution. Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Medium: pH 6.8 Phosphate buffer; 900 mL.

Apparatus 2: 50 rpm.

Procedure—At the end of 45 minutes, determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with *Medium*, in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a second 100-mL volumetric flask, dilute with *Medium*, as obtained in the *Buffer stage,* to volume, and mix. This Standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{14}H_{10}Cl_2NNaO_2$ is dissolved.

•(Official April 1, 2006)•2

BRIEFING

Diltiazem Hydrochloride Extended-Release Capsules, *USP 28* page 655 and page 478 of *PF* 30(2) [Mar.–Apr. 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-56

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2 Proceed as directed for ~~*Extended Release Articles—General Drug Release Standard* ⟨724⟩.~~

•*Extended-Release Dosage Forms.*•2

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Times: 3, 9, and 12 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Harmonization

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to the *Acceptance Table* given.

Acceptance Table

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. At 3 hours none of the units is outside the range of 10% to 35% of labeled content; at 9 hours none of the units is outside the range of 45% to 95% of labeled content; and at 12 hours none of the units is less than 65% of labeled content 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. At 3 hours not more than 2 of the 24 units are outside the range of 10% to 35% of labeled content, and these two units must be within the range of 5% to 45% of labeled content; at 9 hours not more than 2 of 24 of the units are outside the range of 45% to 95% of labeled content, and these two units must be within the range of 35% to 100% of labeled content; at 12 hours not more than 2 of the 24 units are less than 65% of labeled content at the final test time, and these two units cannot be less than 60% of labeled content at the final test time.

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

•USP *Dissolution Test 4.*•$_2$
Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*
Times: 4, 8, 12, and 24 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
4	between 10% and 25%
8	between 35% and 60%
12	between 55% and 80%
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.*~~

•USP *Dissolution Test 5.*•$_2$
Medium: 0.05 M phosphate buffer, pH 7.2; 900 mL.
Apparatus 2: 50 rpm.
Procedure—Proceed as directed under *Test 1.*
Times: 1, 3, and 8 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 15%
3	between 45% and 70%
8	not less than 80%

TEST 10—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 10.*~~

•USP *Dissolution Test 10.*•$_2$
Medium: 0.05 M phosphate buffer, pH 6.5; 900 mL. Prepare the buffer employing the following method. Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5.
Apparatus 1: 100 rpm.
Procedure—Proceed as directed under *Test 1.*
Times: 1, 6, 9, and 24 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 10%
6	between 10% and 30%
9	between 34% and 60%
24	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.*~~

•USP *Dissolution Test 2.*•$_2$
Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*
Times: 1, 4, 10, and 15 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 70% and 90%
15	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 3.*~~

•USP *Dissolution Test 3.*•$_2$
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 100 rpm.
Times: 6, 12, 18, 24, and 30 hours.
Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the

solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 85%

TEST 6—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 6.*~~

•USP *Dissolution Test 6.*•$_2$

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 4, 8, 12, and 16 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
2	not more than 25%
4	between 25% and 50%
8	between 60% and 85%
12	not less than 70%
16	not less than 80%

TEST 7—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 7.*~~

•USP *Dissolution Test 7.*•$_2$

Medium: pH 4.2 acetate buffer; 900 mL. Prepare the buffer by employing the following method. Transfer 115 mL of acetic acid to a 10-L volumetric flask, dilute with water to volume, and mix (Solution A). Transfer 165.4 g of anhydrous sodium acetate to a 10-L volumetric flask, dilute with water to volume, and mix (Solution B). Mix 4410 mL of Solution A with 1590 mL of Solution B. Adjust, if necessary, with the addition of Solution A or Solution B to a pH of 4.2 ± 0.05.

Apparatus 2: 100 rpm.

Times: 1, 4, 10, and 15 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration ofUSP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 10%
4	between 15% and 35%
10	between 65% and 85%
15	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 8.*~~

•USP *Dissolution Test 8.*•$_2$

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 4, 10, and 15 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 60% and 90%
15	not less than 80%

TEST 9—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 9.*~~

•USP *Dissolution Test 9.*•$_2$

NOTE—Perform the test separately in each of the two media.

Medium 1: 0.1 N hydrochloric acid; 900 mL.

Medium 2: simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of 7.5 ± 0.1; 900 mL.

Apparatus 2: 75 rpm.

Time for Medium 1: 2 hours.

Times for Medium 2: 2, 12, 18, and 24 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with the appropriate *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved (*Medium 1*)	Amount dissolved (*Medium 2*)
2	between 0% and 5%	between 20% and 45%
12		between 35% and 55%
18		not less than 60%
24		not less than 80%

TEST 11—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 11.*~~

•USP *Dissolution Test 11.*•$_2$

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 3.*

Times: 1, 6, 12, and 18 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 10%
6	between 30% and 40%
12	between 36% and 58%
18	not less than 85%

TEST 12—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 12.*~~

•USP *Dissolution Test 12.*•2
Proceed as directed for ~~*Extended-Release Articles—General Drug Release Standard* ⟨724⟩.~~

•*Extended-Release Dosage Forms.*•2
Medium and *Procedure*—Proceed as directed under *Test 1.*
Apparatus 1: 100 rpm.
Times: 2, 8, 14, and 24 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	not less than 65%
24	not less than 80%

TEST 13—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 13.*~~

•USP *Dissolution Test 13.*•2
Proceed as directed for ~~*Extended-Release Articles—General Drug Release Standard* ⟨724⟩.~~

•*Extended-Release Dosage Forms.*•2
Medium and *Procedure*—Proceed as directed under *Test 1.*
Apparatus 1: 100 rpm.
Times: 2, 8, 14, and 24 hours.
Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	between 60% and 80%
24	not less than 80%

■TEST 14—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 14.* Proceed as directed for *Extended-Release Articles—General Drug Release Standard* under the general chapter *Drug Release* ⟨724⟩~~•USP *Dissolution Test 14.* Proceed as directed for *Extended-Release Dosage Forms.*•2

Medium, Apparatus, Times, and *Procedure*—Proceed as directed under *Test 3.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩~~•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 80%

■1S (*USP28*)

•(Official April 1, 2006)•2

BRIEFING

Dirithromycin Delayed-Release Tablets, *USP 28* page 676—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-57

Change to read:

~~**Drug release,** *Method B* ⟨724⟩—~~

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2
ACID STAGE—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 10-mesh basket; 100 rpm.

Xanthydrol TS—[NOTE Prepare this solution daily.] To about 150 mg of xanthydrol in a 100-mL volumetric flask, add 10 mL of glacial acetic acid, and swirl to dissolve. Dilute with hydrochloric acid to volume, and mix.

Standard solution—Quantitatively dissolve an accurately weighed quantity of USP Dirithromycin RS in 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.28 mg per mL.

Procedure—After 2 hours of operation, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessel, and subject each Tablet to the test in the *Buffer stage*. Separately add 0.50 mL of acetic anhydride to 0.50 mL of the filtered solution under test and to 0.50 mL of the *Standard solution*, and mix. Add 5.0 mL of glacial acetic acid, allow to stand for 5 minutes, then add 0.50 mL of *Xanthydrol TS*, and allow 30 minutes for color development. Determine the amount of $C_{42}H_{78}N_2O_{14}$, including the 16*R*- and 16*S*-epimers, dissolved by employing UV absorption at the wavelength of maximum absorbance at about 540 nm.

BUFFER STAGE—

Medium: pH 6.8 phosphate buffer; 900 mL.

Procedure—Proceed as directed for *Acid stage* beginning with "Separately add 0.50 mL of acetic anhydride".

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{42}H_{78}N_2O_{14}$, including the 16*R*- and 16*S*-epimers, is dissolved in 45 minutes.

•(Official April 1, 2006)•2

BRIEFING

Disopyramide Phosphate Extended-Release Capsules, *USP 28* page 678—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-58

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets USP ~~*Drug Release Test 1*~~

•*Dissolution Test 1*•2

pH 2.5, 0.1 M Phosphate buffer—Dissolve 272 g of monobasic potassium phosphate in 20 L of water, and adjust with hydrochloric acid to a pH of 2.50 ± 0.04. [NOTE—Do not adjust back to pH 2.50 with base if too much acid is added. It is imperative that the ionic strength of the buffer be controlled.]

Medium: pH 2.5, 0.1 M Phosphate buffer; 1000 mL.

Apparatus 1: 100 rpm.

Times: 1 hour; 2 hours; 5 hours; 12 hours.

Procedure—Filter 10 mL of the solution under test at the required test points. Determine the amount of disopyramide ($C_{21}H_{29}N_3O$) dissolved from UV absorbances at the wavelength of maximum absorbance at about 261 nm of this solution, suitably diluted with *Medium*, if necessary, using *Medium* as the blank, in comparison with a Standard solution having a known concentration of USP Disopyramide Phosphate RS dissolved in *Medium*.

Tolerances—The percentage of the labeled amount of disopyramide ($C_{21}H_{29}N_3O$) dissolved is within the range stated at each of the following times.

Time (hours)	Amount dissolved
1	between 5% and 25%
2	between 17% and 43%
5	between 50% and 80%
12	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP ~~*Drug Release Test 2*~~

•*Dissolution Test 2.*•2

pH 2.5, 0.1 M Phosphate buffer, and *Procedure*—Proceed as directed for *Test 1*.

Medium—Prepare as directed for *Test 1;* 900 mL.

Apparatus 2: 100 rpm.

Times and *tolerances:*

Time (hours)	Amount dissolved
1	between 5% and 30%
4	between 40% and 65%
8	between 60% and 90%
12	not less than 75%

•(Official April 1, 2006)•2

Harmonization

BRIEFING

Divalproex Sodium Delayed-Release Tablets, *USP 28* page 679 and page 835 of *PF* 30(3) [May–June 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-59

Change to read:

~~**Drug release,** *Method B*~~ ■1S *(USP28)* ~~⟨724⟩~~ —

•**Dissolution** ⟨711⟩—•2

~~*pH 1.2, 0.08 N Hydrochloric acid*—Add 40 mL of Hydrochloric acid to 5000 mL of water. Adjust with 2 N hydrochloric acid to a pH of 1.2, dilute with water to 6.0 liters, and mix.~~

~~*pH 7.5 Phosphate buffer*—Dissolve 40.83 g of monobasic potassium phosphate and 9.84 g of sodium hydroxide in 5000 mL of water. just with *pH 1.2, 0.08 N Hydrochloric acid* to a pH of 7.5, dilute with water to 6.0 liters, and mix.~~

~~*Medium*—Proceed as directed for *Method B,* observing the following exceptions. Perform *Acid Stage* testing, using 900 mL of *pH 1.2, 0.08 N Hydrochloric acid,* for 1 hour; and perform *Buffer Stage* testing, using 900 mL of *pH 7.5 Phosphate buffer,* for not less than 1 hour.~~

~~*Apparatus 2:* 50 rpm.~~

~~*Times:* 1 and 2 hours.~~

■ACID STAGE—

Medium: 0.08 N hydrochloric acid (prepared by adding 40 mL of hydrochloric acid to 5000 mL of water, adjusting with 2 N hydrochloric acid to a pH of 1.2, and diluting with water to 6000 mL); 900 mL.

Apparatus 2: 50 rpm.

Time: 1 hour.

Procedure—At the end of 1 hour, carefully transfer the Tablet to a dissolution vessel containing the *Medium* of the *Buffer stage*. [NOTE—Do not perform an analysis of the *Medium* in the *Acid stage*.]

BUFFER STAGE—

Medium: pH 7.5 phosphate buffer (prepared by dissolving 40.83 g of monobasic potassium phosphate and 9.84 g of sodium hydroxide in 5000 mL of water, adjusting with 0.08 N hydrochloric acid to a pH of 7.5, and diluting with water to 6000 mL); 900 mL.

Apparatus 2: 50 rpm.

Time: 1 hour.■1S *(USP28)*

Determine the amount of $C_8H_{16}O_2$ dissolved ■in the *Buffer stage*■1S *(USP28)* by employing the following method.

Citrate buffer—Dissolve 0.5 g of citric acid monohydrate and 0.4 g of dibasic sodium phosphate in 1.0 L of water.

Potassium phosphate buffer—Dissolve 6.8 g of monobasic potassium phosphate and 1.7 g of sodium hydroxide in 1.0 L of water. Adjust with phosphoric acid to a pH of 7.4 ± 0.1.

Mobile phase—Prepare a mixture of *Citrate buffer, Potassium phosphate buffer,* and acetonitrile (35 : 35 : 30). Adjust with phosphoric acid to a pH of 3.0 ± 0.1, and mix. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Valproic Acid RS in the ~~*pH 7.5 Phosphate buffer*~~

■*Medium*■1S *(USP28)* used in the *Buffer stage,* having a known concentration of about 0.12 mg per mL. [NOTE—A volume of acetonitrile not exceeding 10.0% of the total volume may be used to dissolve the USP Valproic Acid RS.]

Test solution—If necessary, dilute a portion of each filtered solution under test with the ~~*pH 7.5 Phosphate buffer*~~

■*Medium*■1S *(USP28)* used in the *Buffer stage* to obtain a solution having a concentration of about 0.12 mg per mL.

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 4-µm packing L11. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard solution,* 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 that 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of valproic acid ($C_8H_{16}O_2$) dissolved by the formula:

$$900CD(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Valproic Acid RS 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 valproic acid obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_8H_{16}O_2$ is dissolved in ~~2 hours.~~

■1 hour in the *Buffer stage.*■1S *(USP28)*

•(Official April 1, 2006)•2

Harmonization

BRIEFING

Doxycycline Hyclate Delayed-Release Capsules, *USP 28* page 700—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-44

Change to read:

~~**Drug release,** *Method B* ⟨724⟩~~ —

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—[NOTE—Conduct the test by transferring the contents of each Capsule to the individual basket units of the apparatus.]

Medium: 0.06 N hydrochloric acid; 900 mL.

Apparatus 1: 50 rpm.

Time: 20 minutes.

Diluting solvent: 0.1 N hydrochloric acid.

Procedure—Determine the amount of $C_{22}H_{24}N_2O_8$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 345 nm on filtered portions of the solution under test, suitably diluted with *Diluting solvent*, in comparison with a Standard solution having a known concentration of about 0.01 mg of USP Doxycycline Hyclate RS per mL in *Diluting solvent*.

Tolerances—Level 1 (6 Capsules tested): No individual value exceeds 50% dissolved. *Level 2* (6 Capsules tested): Not more than 2 individual values of 12 tested are greater than 50% dissolved.

BUFFER STAGE—[NOTE—Conduct this stage of testing on separate specimens, selecting Capsules that were not previously subjected to *Acid-stage* testing and transferring the contents of each Capsule to the individual basket units of the apparatus.]

Medium: pH 5.5 neutralized phthalate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 1000 mL.

Apparatus 1: 50 rpm.

Time: 30 minutes.

Diluting solvent: 0.1 N hydrochloric acid.

Procedure—Determine the amount of $C_{22}H_{24}N_2O_8$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 345 nm on filtered portions of the solution under test, suitably diluted with *Diluting solvent*, in comparison with a Standard solution having a known concentration of about 0.01 mg of USP Doxycycline Hyclate RS per mL in *Diluting solvent*.

Tolerances—Not less than 85% *(Q)* of the labeled amount of $C_{22}H_{24}N_2O_8$ is dissolved in 30 minutes.

•(Official April 1, 2006)•2

BRIEFING

Erythromycin Delayed-Release Capsules, *USP 28* page 758—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-29

Change to read:

~~**Drug release,** *Method B* ⟨724⟩~~ —

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

Apparatus 1: 50 rpm.

Times: 60 minutes for *Acid Stage;* 60 minutes for *Buffer Stage*.

Procedure—Transfer the contents of 1 Capsule to the apparatus. Proceed as directed for *Acid Stage*, 900 mL of 0.06 N hydrochloric acid being placed in the vessel instead of 1000 mL of 0.1 N hydrochloric acid, and the apparatus being operated for 60 minutes instead of 2 hours. Do not perform an analysis at the end of the *Acid stage*. Continue as directed for *Buffer Stage*, 900 mL of the pH 6.8 phosphate buffer being used instead of 1000 mL. Determine the amount of $C_{37}H_{67}NO_{13}$ dissolved after 120 minutes by assaying a filtered portion of the solution under test as directed under *Antibiotics—Microbial Assays* ⟨81⟩.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{37}H_{67}NO_{13}$ is dissolved in 120 minutes.

•(Official April 1, 2006)•2

BRIEFING

Erythromycin Delayed-Release Tablets, *USP 28* page 762—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-30

Change to read:

Labeling—The label indicates that the Tablets are enteric-coated. The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Harmonization

Change to read:

~~**Drug release,** *Method B* ⟨724⟩—~~

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

TEST 1— If the product complies with this test, the labeling indicates that it meets USP ~~*Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Apparatus 1: 100 rpm.
Times: 60 minutes, Stage 1; 60 minutes, Stage 2.
Acid stage—Using 900 mL of simulated gastric fluid TS (prepared without pepsin) in place of 0.1 N hydrochloric acid, conduct this stage of the test for 1 hour, and do not perform an analysis of the medium.
Buffer stage—Using 900 mL of 0.05 M pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*), conduct this stage of the test for 60 minutes.
Test solution—If necessary, dilute a filtered portion of the solution under test with *Dissolution Medium* to obtain a solution having a concentration of about 0.28 mg of erythromycin per mL, and mix.
Procedure—Transfer a 2.0-mL portion of the *Test solution* to a suitable separator. Add 6 mL of pH 1.2 buffer (see *Solutions* in the section *Reagents*, *Indicators*, *and Solutions*), and 8 mL of a solution of bromocresol purple, prepared by dissolving 1 g of bromocresol purple in 1 L of pH 4.5 phosphate buffer, and mix. Extract with 40.0 mL of chloroform. Determine the amount of $C_{37}H_{67}NO_{13}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 410 nm using the chloroform extracts. Similarly prepare a Standard solution, having a known concentration of USP Erythromycin RS, and treat similarly.
TEST 2— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2
Proceed as directed under *Test 1*, except to use *Apparatus 2* at 75 rpm.

•(Official April 1, 2006)•2

BRIEFING

Conjugated Estrogens Tablets, *USP 28* page 778—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-31

Change to read:

Labeling—The labeling indicates the Tablet strength and states with which in vitro ~~*Drug Release Test*~~

•*Dissolution Test*•2
the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
Proceed as directed for ~~*Extended-Release Articles—General Drug Release Standard.*~~

•*Extended-Release Articles.*•2
TEST 1 (for products labeled as 0.3-, ▲0.45-,▲*USP28* and 0.625-mg tablets)—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Mobile phase—Prepare a filtered and degassed mixture of 0.025 M monobasic potassium phosphate and acetonitrile (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard solution—Transfer 10 Tablets to a 1000-mL volumetric flask, dilute with water to volume, and stir vigorously by mechanical means for at least 3 hours. Pipet a filtered 100-mL aliquot of the solution into a 900-mL volumetric flask, and dilute with water to volume.
Test solution—Filter a portion of the solution under test. [NOTE—It is recommended that the filters selected be tested for binding affinity.]
Chromatographic system—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 3.0-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.9 for equilin sulfate and 1.0 for estrone sulfate, the estrone sulfate peak being the last major peak in the chromatogram; the resolution, *R,* between equilin sulfate and estrone sulfate is not less than 1.5; and the relative standard deviation for the estrone sulfate peak is not more than 1.5%. [NOTE—If estrone is present it may be retained on the column for a period longer than 50 minutes and interfere in later chromatographic runs.]
Procedure—Separately inject equal volumes (between 20 and 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the estrone sulfate peaks. Calculate the percentage of estrone sodium sulfate released 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.
Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

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

TEST 2 (for products labeled as 0.9-mg tablets)—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2

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

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

•*Acceptance Table 2.*•2

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

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

•USP *Dissolution Test 3.*•2

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

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

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

•(Official April 1, 2006)•2

BRIEFING

Felodipine Extended-Release Tablets, *USP 28* page 808 and page 482 of *PF* 30(2) [Mar.–Apr. 2004]—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-32

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

▲*Medium:* pH 6.5 phosphate buffer with 1% of sodium lauryl sulfate (Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a 5000-mL volumetric flask. Add approximately 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5. Dilute with water to volume, and mix well); 500 mL.

Apparatus 2: 50 rpm.

Times: 2, 6, and 10 hours.

Buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and methanol (2 : 2.5 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL.

Standard solution—Dilute an accurately measured volume of the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about 60% dissolution of a single Tablet in 500 mL of *Medium.*

Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1*). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (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 quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved in the *Medium* by the formula:

$$CD(r_U / r_S),$$

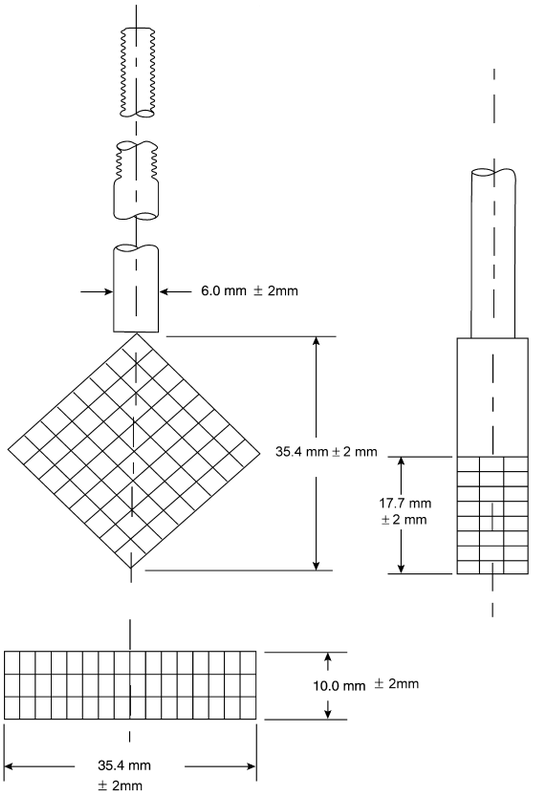
Harmonization

in which C is the concentration, in mg per mL, of USP Felodipine RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the felodipine peak areas obtained from the *Test solution* and the *Standard solution,* respectively.▲*USP28*

Tolerances—The percentages of the labeled amount of $C_{18}H_{19}ClNO_4$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~ ♣ ~~under *Drug Release* ⟨724⟩~~.▲*USP28*

•*Acceptance Table 2.*●2

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 42% and 68%
10	not less than 75%



NOTES

1. Rod and Basket with a Tablet cover placed in the horizontal diagonal of the basket.
2. Basket and Tablet cover material; stainless steel.
3. Basket gauze wire size: 8 mesh.

▲Fig. 1. Stationary Tablet Basket▲*USP28*

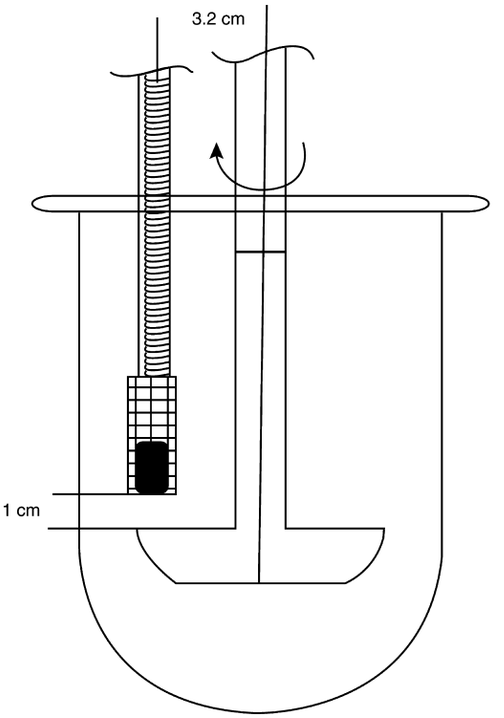


Fig. 2. Drug Release Stationary Tablet Basket Configuration Diagram

•(Official April 1, 2006)•2

BRIEFING

Ferrous Fumarate and Docusate Sodium Extended-Release Tablets, *USP 28* page 818—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-33

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

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.

Tolerances—The percentages of the labeled amount of Fe (II) dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩~~.

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 40% and 75%
3	not less than 80%

•(Official April 1, 2006)•2

Harmonization

BRIEFING

Garlic Delayed-Release Tablets, *USP 28* page 2090—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-34

Change to read:

Allicin release~~— Proceed as directed for *Delayed-Release (Enteric-Coated) Articles, Method A* under *Drug Release* ⟨724⟩.~~

•Proceed as directed for *Method A* in *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms* under *Dissolution* ⟨711⟩.•[2]

Place a number of Tablets, equivalent to about 5 mg of potential allicin, in each vessel.

Apparatus 2: 100 rpm.

Time: 60 minutes for the *Buffer stage.*

Mobile phase, *Crude alliinase solution*, *Blank solution,* and *Chromatographic system*—Proceed as directed in the test for *Content of potential allicin.*

Standard solution—Dissolve an accurately weighed quantity of USP Alliin RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 50 µg per mL. Transfer 1.0 mL of this solution to a 5-mL volumetric flask containing 100 µL of *Crude alliinase solution*, mix, and allow to stand for 5 minutes at room temperature. Dilute with water to volume, and pass through a membrane filter having a 0.45-µm or finer porosity.

Test solution—Transfer 1.0 mL of the solution under test to a test tube containing 50 µL of 0.21 M carboxymethoxylamine hemihydrochloride. [NOTE—The solution must be transferred immediately upon removal from the dissolution vessel in order to inhibit the alliinase enzyme.]

Procedure—[NOTE—Do not perform the allicin determination in the *Acid stage.*] Determine the amount of allicin released by injecting 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 allicin peaks. Calculate the amount, in µg, of allicin released in the *Buffer stage* by the formula:

$$1050C(162.26/354.42)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Alliin RS in the *Standard solution;* 162.26 is the molecular weight of allicin; 354.42 is twice the molecular weight of alliin; and r_U and r_S are the peak responses for allicin obtained from the *Test solution* and the *Standard solution,* respectively. [NOTE—Q is the percentage of the labeled amount of potential allicin released only in the *Buffer stage.*]

•(Official April 1, 2006)•[2]

BRIEFING

Hydroxyzine Hydrochloride Tablets, *USP 28* page 982—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—4

Change to read:

Dissolution ⟨711⟩—

▲TEST 1—

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 *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.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: water, 250 mL.

Apparatus 3:~~(see *Drug Release* ⟨724⟩).~~

••[2]

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 *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.▲*USP28*

•(Official April 1, 2006)•[2]

BRIEFING

Indomethacin Extended-Release Capsules, *USP 28* page 1014—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS— 42035-52

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: pH 6.2 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 750 mL.
Apparatus 1: 75 rpm.
Times: 1, 2, 4, 6, 12, and 24 hours.
Procedure—Determine the amount of Indomethacin dissolved from UV absorbances at the wavelength of maximum absorbance at about 318 nm on filtered portions of the solution under test, diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Indomethacin RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 25%
2	between 20% and 40%
4	between 35% and 55%
6	between 45% and 65%
12	between 60% 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.*~~

•USP *Dissolution Test 2.*•2
Medium,Apparatus, and *Procedure*—Proceed as directed under *Test 1*, except to use 900 mL of *Medium*.
Times: 1, 2, 4, and 12 hours.
Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 12% and 32%
2	between 27% and 52%
4	between 50% and 80%
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.*~~

•USP *Dissolution Test 3.*•2
Medium: pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 750 mL.
Apparatus and *Procedure*—Proceed as directed under *Test 1.*
Times: 1, 2, 4, 6, 12, and 24 hours.
Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 15% and 40%
2	between 35% and 55%
4	between 55% and 75%
6	between 65% and 85%
12	not less than 75%
24	not less than 85%

•(Official April 1, 2006)•2

BRIEFING

Isosorbide Dinitrate Extended-Release Capsules, *USP 28* page 1086—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-37

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
~~Proceed as directed for *Method B* under *Delayed-release Articles—General Drug Release Standard*, except to operate the apparatus in the acid medium for 1 hour instead of 2 hours and to use *Acceptance Table 1* under *Extended-release Articles—General Drug Release Standard.*~~

•Proceed as directed for *Method B* in *Delayed-Release Dosage Forms* in *Procedure, Apparatus 1 and Apparatus 2,* except to operate the apparatus in the acid medium for 1 hour instead of 2 hours and to use *Acceptance Table 2* in *Extended-Release Dosage Forms* in *Interpretation*.•2
Apparatus 2: 50 rpm.
Times: 2, 4, and 8 hours.
Determine the amount of $C_6H_8N_2O_8$ dissolved using the following method.
Mobile phase—Prepare a filtered and degassed mixture of 0.05 M monobasic potassium phosphate and acetonitrile (52 : 48). Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Harmonization

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, and record the chromatograms as directed for *Procedure:* the tailing factor is not more than 2.5; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of a filtered portion of the solution under test, and record the chromatograms. Determine the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium and similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_6H_8N_2O_8$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

[NOTE—The test times given are cumulative, beginning with the 1 hour in the acid medium.]

Time (hours)	Amount dissolved
2	between 10% and 30%
4	between 40% and 75%
8	not less than 75%

•(Official April 1, 2006)•$_2$

BRIEFING

Isosorbide Dinitrate Extended-Release Tablets, *USP 28* page 1087—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-38

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•$_2$

Medium: water; 500 mL.
Apparatus 2: 50 rpm.
Times: 1, 2, 4, and 6 hours.

Determine the amount of $C_6H_8N_2O_8$ dissolved, using the following method.

pH 3.0 Buffer solution—Add 6.6 g of ammonium sulfate, accurately weighed, to 500 mL of water. Adjust with 1 N sulfuric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *pH 3.0 Buffer solution* (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a UV wavelength detector and a 5-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, and record the chromatograms as directed for *Procedure:* the tailing factor is not more than 2.5; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of a filtered portion of the solution under test, and record the chromatograms. Determine the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_6H_8N_2O_8$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 15% and 30%
2	between 50% and 70%
4	between 65% and 85%
6	not less than 75%

•(Official April 1, 2006)•$_2$

BRIEFING

Lansoprazole Delayed-Release Capsules, *USP 28* page 1111—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-39

Change to read:

~~**Drug release,** *Method A* ⟨724⟩~~—

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method A* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•$_2$

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 500 mL.
Apparatus 2: 75 rpm.
Time: 60 minutes.

Procedure—Withdraw a 25-mL aliquot and then proceed immediately as directed for *Test solution* in the *Buffer stage,* leaving the remaining 475 mL in the vessel for use in the *Buffer stage*. Using a filtered portion of the aliquot, determine the amount of $C_{16}H_{14}F_3N_3O_2S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 306 nm, using *Acid stage medium* as the blank. Concomitantly determine the absorbance of the *Acid stage* test solution in comparison with a solution of USP Lansoprazole RS, having a known concentration equivalent to about 8% of the labeled amount of lansoprazole dissolved per 500 mL of *Acid stage medium.* [NOTE—A volume of methanol not to exceed 0.5% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Acid stage medium.*]

Tolerances—Not more than 10% of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ is dissolved in 60 minutes.

BUFFER STAGE—

Buffer concentrate—Transfer 65.4 g of monobasic sodium phosphate, 28.2 g of sodium hydroxide, and 12 g of sodium dodecyl sulfate to a suitable container, and add enough water to dissolve. Dilute with water to 4 L, and mix well.

Blank solution—Prepare a mixture of *Acid stage medium* and *Buffer concentrate* (19 : 17). Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Test solution—Add 425 mL of *Buffer concentrate* to the remaining 475 mL of solution in each vessel from the *Acid stage.* Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{16}H_{14}F_3N_3O_2S$ dissolved in filtered portions of the *Test solution*, using the difference between the absorbances at the wavelengths of about 286 nm and 650 nm, with *Blank solution* as the blank. Concomitantly determine the absorbances of the *Test solution* in comparison with the solution of USP Lansoprazole RS having a known concentration equivalent to about 70% of the labeled amount of lansoprazole dissolved in 900 mL of *Blank solution.* [NOTE—An amount of methanol not to exceed 2% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Blank solution.*]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ is dissolved in 60 minutes.

•(Official April 1, 2006)•2

obtain a solution having a known concentration of about 10 µg of USP Liothyronine RS per mL. Dilute a portion of this solution quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 µg of USP Liothyronine RS per mL.

Test solution—Transfer 20 mL of the solution under test to a centrifuge tube, and centrifuge until a clear supernatant is obtained.

Resolution solution—Prepare a solution of USP Liothyronine RS and USP Levothyroxine RS in *Ammoniated solution* having known concentrations of about 10 µg of each USP Reference Standard per mL. Dilute with water to obtain a concentration of about 0.5 µg of each USP Reference Standard per mL.

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 L10. The flow rate is about 2 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between liothyronine and levothyroxine is not less than 3.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 200 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 $C_{15}H_{12}I_3NO_4$ dissolved.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}I_3NO_4$ is dissolved in 45 minutes.

•(Official April 1, 2006)•2

BRIEFING

Liothyronine Sodium Tablets, *USP 28* page 1138—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-40

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing liothyronine sodium are to be made of glass.]

Medium: pH 10.0 ± 0.05 alkaline borate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 250 mL.

Apparatus 3: ~~(see *Drug Release* ⟨724⟩.)~~

•
•2
30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass reciprocating cylinder.

Time: 45 minutes.

Determine the amount of liothyronine sodium ($C_{15}H_{12}I_3NO_4$) dissolved by employing the following method.

Ammoniated solution—Add 0.05 mL of ammonium hydroxide to 200 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55 : 45) that contains 1 mL of phosphoric acid in each 1000 mL of solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Liothyronine RS in *Ammoniated solution*, and dilute quantitatively, and stepwise if necessary, with *Ammoniated solution* to

BRIEFING

Lithium Carbonate Extended-Release Tablets, *USP 28* page 1142—See briefing under *Aspirin Delayed-Release Capsules.* In addition, minor editorial style changes have been made.

(BPC: W. Brown) RTS—42035-41

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution**⟨711⟩—•2
TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: dilute hydrochloric acid (7 in 1000); 800 mL.
Apparatus 1: 100 rpm.
Times: 15, 45, 90, and 120 minutes.

Harmonization

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 *Medium* if necessary, and using *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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 2.*•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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 3.*•2

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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 4.*•2

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.*~~

•*Acceptance Table 2.*•2

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 80%

•(Official April 1, 2006)•2

BRIEFING

Mesalamine Extended-Release Capsules, *USP 28* page 1221 and page 896 of *PF* 30(3) [May–June 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-42

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

Medium: 0.05 M pH 7.5 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate and 1 g of sodium hydroxide in water to make 1000 mL of solution, and adjusting with 10 N sodium hydroxide to a pH of 7.50 ± 0.05;

■900 mL.■1S (*USP28*)

Apparatus 2: 100 rpm.

Times: 1, 2, 4, and 8 hours.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 330 nm on filtered portions of the solution under test suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Mesalamine RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_7H_7NO_3$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 5% and 25%
2	between 30% and 50%
4	between 60% and 90%
8	not less than 85%

•(Official April 1, 2006)•2

BRIEFING

Mesalamine Delayed-Release Tablets, *USP 28* page 1222—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-43

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•$_2$

pH 6.0 Phosphate buffer—Transfer about 43.35 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide to a 2-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.

Sodium hydroxide solution—Transfer 133.6 g of sodium hydroxide to a 2-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Media: 0.1 N hydrochloric acid, 500 mL for *Acid stage; pH 6.0 Phosphate buffer*, 900 mL for *Buffer stages*.

Apparatus 2: 100 rpm for *Acid stage* and for *Buffer stage 1;* 50 rpm for *Buffer stage 2*.

Times: 2 hours for *Acid stage;* 1 hour for *Buffer stage 1;* 90 minutes for *Buffer stage 2*.

ACID STAGE—After 2 hours of operation, withdraw an aliquot of the fluid, discard the remaining solution, and retain the Tablets in proper order, so that each will be returned to its respective vessel later on. Blot the Tablets with a paper towel to dry, and proceed immediately as directed for *Buffer stage 1*.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 302 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 Mesalamine RS, equivalent to about 1% of the labeled amount of $C_7H_7NO_3$, in the same *Medium*.

Tolerances—The percentage of the labeled amount of $C_7H_7NO_3$ dissolved from the units tested conforms to the *Acceptance Table* shown below. Continue testing through all levels unless the results conform at an earlier level.

BUFFER STAGE 1—[NOTE—Use buffer that has been equilibrated to a temperature of 37 ± 0.5°.] Transfer *pH 6.0 Phosphate buffer* to each of the dissolution vessels, and place each Tablet from the *Acid stage* into its respective vessel. After 1 hour remove a 50-mL aliquot, and proceed immediately as directed for *Buffer stage 2*.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 330 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 Mesalamine RS, equivalent to about 1% of the labeled amount of $C_7H_7NO_3$, in the same *Medium*.

Tolerances—The percentage of the labeled amount of $C_7H_7NO_3$ dissolved from the units tested conforms to the *Acceptance Table* shown below. Continue testing through all levels unless the results conform at an earlier level.

Acceptance Table

Level	Number Tested	Criteria
L_1	6	No individual value exceeds 1% dissolved.
L_2	6	Average of the 12 units ($L_1 + L_2$) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved.
L_3	12	Average of the 24 units ($L_1 + L_2 + L_3$) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved.

BUFFER STAGE 2—Add 50 mL of *Sodium hydroxide solution* to each dissolution vessel to adjust to a pH of 7.2, and continue the run.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 332 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 Mesalamine RS in the same *Medium*.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_7H_7NO_3$ is dissolved. The requirements are met if the quantities dissolved from the product conform to ~~*Acceptance Table 3* under *Drug Release*⟨724⟩.~~

•*Acceptance Table 4.*•$_2$

Continue testing through all levels unless the results conform at an earlier level.

•(Official April 1, 2006)•$_2$

BRIEFING

Methylphenidate Hydrochloride Extended-Release Tablets, *USP 28* page 1267 and page 1263 of *PF* 30(4) [July–Aug. 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-8

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•$_2$

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Times: 1 hour; 2 hours; 3.5 hours; 5 hours; 7 hours.

■*Test solution*—Use portions of the solution under test passed through a 0.45-µm polypropylene filter. [NOTE—Do not use glass fiber filters.]■1S *(USP28)*

Harmonization

Procedure—Determine the amount of $C_{14}H_{19}NO_2 \cdot HCl$ dissolved, employing the procedure set forth in the *Assay*, making any necessary volumetric adjustments.

Tolerances—The percentages of the labeled amount of $C_{14}H_{19}NO_2 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 25% and 45%
2	between 40% and 65%
3.5	between 55% and 80%
5	between 70% and 90%
7	not less than 80%

•(Official April 1, 2006)•$_2$

BRIEFING

Metoprolol Succinate Extended-Release Tablets, *USP 28* page 1280—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-9

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•$_2$

Medium: pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents*, *Indicators*, *and Solutions*); 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, 8, and 20 hours.

Determine the amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved by employing the following method.

pH 3.0 Phosphate buffer, *Mobile phase*, and *Standard solution*—Proceed as directed in the test for *Uniformity of dosage units.*

Procedure—Proceed as directed in the test for *Uniformity of dosage units*, except to use 5.0 mL of a filtered portion of the solution under test as the *Test solution*, and *Medium* as the blank, in comparison with a Standard solution having a known concentration of USP Metoprolol Succinate RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 25%
4	between 20% and 40%
8	between 40% and 60%
20	not less than 80%

•(Official April 1, 2006)•$_2$

BRIEFING

Morphine Sulfate Extended-Release Capsules, *USP 28* page 1314 and page 1822 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-10

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•$_2$

pH 7.5 Phosphate buffer—Dissolve 6.8 g of monobasic potassium phosphate and 1.6 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid or 2 N sodium hydroxide to a pH of 7.5.

Medium—Proceed as directed for ~~*Method B* under *Delayed-Release (Enteric-Coated) Articles—General Drug Release Standard,*~~

•*Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,* •$_2$ observing the following exceptions. Perform *Acid stage* testing, using 500 mL of 0.1 N hydrochloric acid for 1 hour; and perform *Buffer stage* testing, using 500 mL of *pH 7.5 Phosphate buffer* for not less than 8 hours.

Apparatus 1: 100 rpm.

Times: 1, 4, 6, and 9 hours.

Determine the amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and glacial acetic acid (72 : 28 : 1), containing 0.73 g of sodium 1-heptanesulfonate. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of phenol and USP Morphine Sulfate RS in *Mobile phase* to obtain a solution containing about 0.1 mg of each per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Morphine Sulfate RS in *pH 7.5 Phosphate buffer,* and dilute quantitatively, and stepwise if necessary, with *pH 7.5 Phosphate buffer* to obtain a solution having a known concentration corresponding to that of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 284-nm detector and a 3.9-mm × 30.0-cm column that contains 10-µm packing L1. The flow rate is about 2 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 phenol and 1.0 for morphine sulfate; the resolution, *R,* between the phenol and

morphine sulfate peaks is not less than 2.0; the tailing factor for the morphine sulfate peak 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 25 µL) of the *Standard solution* and the filtered portion of the solution under test into the chromatograph, record the chromatograms, and measure the peak responses. Determine the amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved from the measured peak responses.

Tolerances—The percentage of the labeled amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved in 1 hour conforms to ~~*Acceptance Table 2.*~~

•*Acceptance Table 3.*•$_2$
The percentages of the labeled amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved at the other times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 10%
4	between 25% and 50%
6	between 50% and 90%
9	not less than 85%

•(Official April 1, 2006)•$_2$

BRIEFING

Nicotine Transdermal System, *USP 28* page 1371—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-11

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: Phosphoric acid solution (1 in 1000); 250 mL, in a tall-form beaker.

Apparatus 7—Proceed as directed in the chapter, using the transdermal system holder—cylinder ~~(see *Figure 7b*).~~

•(see *Figure 4b*).•$_2$
Center the Transdermal System onto a dry, unused 10-cm × 10-cm piece of Cuprophan dialysis membrane with the adhesive side against the membrane, taking care to eliminate air bubbles between the membrane and the release surface. Attach the membrane to the cylinder using two Parker O-rings, such that one of the borders of the transdermal system is aligned to the groove and it is wrapped around the cylinder. The filled beakers are weighed and pre-equilibrated to 32.0 ± 0.3°, prior to immersing the test sample. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of 2.0 ± 0.1 cm. 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°. At the end of each release interval, allow the beakers to cool to room temperature, make up for evaporative losses by adding water to obtain the original weight, and mix. This solution is the final *Test solution*.

Times: 2, 12, and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Transfer 0.2 mL of *N,N*-dimethyloctylamine to a 1-L volumetric flask, add 220 mL of acetonitrile, and mix. Add 300 mL of water, 0.2 mL of glacial acetic acid, 0.20 g of anhydrous sodium acetate, and 0.55 g of sodium 1-dodecanesulfonate, and dilute with water to volume. Mix for 1 hour until clear. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Equilibration of the column may take as long as 3 hours.]

Standard solution—Dissolve an accurately weighed quantity of USP Nicotine Bitartrate Dihydrate RS in *Dissolution Medium*, and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a solution having a known concentration of about 0.142 mg of nicotine bitartrate per mL (or 0.046 mg nicotine as free base per mL). [NOTE—About 80 mL of this solution is required to prepare the *System suitability solution.*]

System suitability solution—Transfer 8 mg (free base) of nicotine to a 100-mL volumetric flask, and dissolve in 10 mL of acetonitrile. Add 5 mL of 30 percent hydrogen peroxide, and allow 15 minutes to react. Dilute with *Dissolution Medium* to volume, and mix. Transfer 20 mL of this solution to a 100-mL volumetric flask, dilute with *Standard solution* 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 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 nicotine and any degradation peaks is not less than 1.1; 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 50 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.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified below, conforms to ~~*Acceptance Table 4.*~~

•*Acceptance Table 1.*•$_2$

Time (hours)	Amount dissolved
0–2	between 31% and 87%
2–12	between 62% and 191%
12–24	between 85% and 261%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Phosphate buffer—Dissolve 40.0 g of sodium chloride, 1.0 g of potassium chloride, 8.66 g of dibasic sodium phosphate, and 1.0 g of monobasic potassium phosphate in 5 L of water.

Medium: Phosphate buffer; 500 mL.

Apparatus 6: 50 rpm, double-sided tape being used to attach the Transdermal System to the cylinder.

Times: 6 and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Proceed as directed in the *Assay.*

System suitability solution—Transfer 1.0 mL of the *System suitability solution*, prepared as directed in the *Assay*, to a 100-mL volumetric flask, dilute with *Dissolution Medium* to volume, and mix.

Standard solution—Pipet 6.0 mL of the *Standard preparation*, prepared as directed in the *Assay*, into a 50-mL volumetric flask, dilute with *Dissolution Medium* to volume, and mix. Dilute quantitatively and stepwise with *Dissolution Medium* to obtain an appropriate final concentration.

Test solution—At each of the test times, withdraw a 2-mL aliquot of the solution under test. [NOTE—Replace the aliquots withdrawn for analysis with fresh portions of *Medium.*]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 12.5-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution* used for the 6-hour interval, and record the peak responses as directed for *Procedure:* the resolution, *R*, between 4,4′-dipyridyl dihydrochloride and nicotine is not less than 5.0; 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 filtered portion of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to ~~*Acceptance Table 4*~~

•*Acceptance Table 1.*•$_2$

Time (hours)	Amount dissolved
6	between 71% and 157%
24	between 156% and 224%

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 5: 50 rpm, the stainless steel disk assembly being replaced with a 5-cm watch glass for an 11-mg Transdermal System and an 8-cm watch glass for a 22-mg Transdermal System.

Times: 1, 2, and 4 hours.

Standard solution—Prepare a solution of USP Nicotine Bitartrate RS in water having a known concentration of nicotine similar to that of the solution under test.

Procedure—Determine the amount of $C_{10}H_{14}N_2$ released by employing UV absorption at the wavelength of maximum absorbance at about 259 nm, in comparison with the *Standard solution*, using water as the blank.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to the following *Acceptance Table*.

Acceptance Table

Level	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 5% of the labeled content outside each of the stated ranges; and none is more than 5% of the 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 5% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 5% of the labeled content below the stated amount at the final test time; and none of the units is more than 10% of the labeled content outside each of the stated ranges or more than 10% of the labeled content below the stated amount at the final test time.

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

Medium: 0.025 N hydrochloric acid; 600 mL.

Apparatus 5: 50 rpm, a convex screen being used to hold the Transdermal System in position during testing.

Times: 4 and 16 hours.

Standard solution and *Procedure*—Proceed as directed for *Procedure* in *Test 3*.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to ~~*Acceptance Table 4*~~

•*Acceptance Table 1.*•$_2$

Time (hours)	Amount dissolved
4	between 36% and 66%
16	between 72% and 112%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.

Phosphate buffer, *Medium*, and *Apparatus*—Proceed as directed under *Test 2*.

Times: 3, 6, and 24 hours.

Mobile phase—Proceed as directed in the *Assay.*

System suitability solution, *Standard solution*, *Test solution*, and *Chromatographic system*—Proceed as directed under *Test 2*.

Procedure—Proceed as directed under *Test 2* except to inject about 30 µL.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to ~~*Acceptance Table 5*~~

•*Acceptance Table 1.*•2

Time (hours)	Amount dissolved
3	between 79% and 112%
6	between 108% and 141%
24	between 156% and 202%

•(Official April 1, 2006)•2

BRIEFING

Nifedipine Extended-Release Tablets, *USP 28* page 1377 and page 1269 of *PF* 30(4) [July–Aug. 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-12

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: water; 500 mL.
Apparatus 7

•(see *Drug Release* ⟨724⟩):•2

■15 to 30 cycles per minute.■1S (*USP28*)
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°.

■At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.■1S (*USP28*)
Times: 4, ~~12, and 24 hours.~~

■8, 12, 16, 20, and 24 hours.■1S (*USP28*)
~~*Diluting solution 1:* a mixture of methanol and acetonitrile (1 : 1).~~
~~*Diluting solution 2:* a mixture of *Diluting solution 1* and water (1 : 1).~~

■*Diluting solution:* a mixture of methanol and water (1 : 1).■1S (*USP28*)
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,*~~

■methanol,■1S (*USP28*)
dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with ~~*Diluting solution 2* 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.~~

■*Diluting solution* to obtain solutions having suitable known concentrations.

Test solution—Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise, if necessary, with *Diluting solution* to obtain a final mixture consisting of equal parts of methanol and water.■1S (*USP28*)
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.~~

■Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Test solution* at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. [NOTE—For the 4-hour time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]■1S (*USP28*)
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.*~~

•*Acceptance Table 2.*●2

~~Time (hours)~~	~~Amount dissolved~~
~~4~~	~~between 5% and 17%~~
~~12~~	~~between 43% and 80%~~
~~24~~	~~not less than 80%~~

■

Time (hours)	Amount dissolved*
4	between 5% and 17%
8	—
12	between 43% and 80%
16	—
20	—
24	not less than 80%

* The amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.■1S (*USP28*)

TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*●2

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L 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 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm, with sinkers (see *Figure 1*).

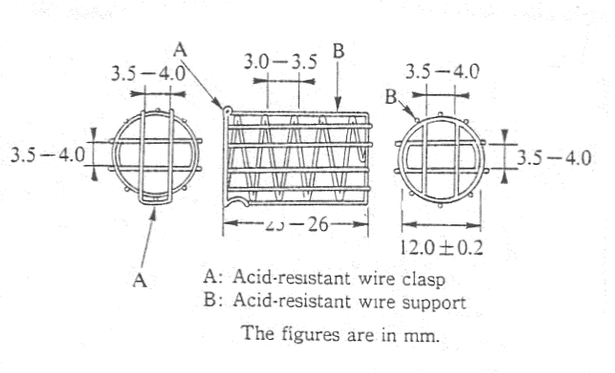


Fig. 1 (printed with permission of the Japanese Pharmacopoeia)

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 *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.*~~

•*Acceptance Table 2.*●2

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.*~~

•USP *Dissolution Test 3.*●2

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5;

■900 mL.■1S (*USP28*)

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. [NOTE—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 *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 *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 0.034 mg of USP Nifedipine RS per mL. [NOTE—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 *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.*~~

•*Acceptance Table 2.*•2

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;

■900 mL.■1S (*USP28*)

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 *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 *Medium* as the blank.

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.

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. [NOTE—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 *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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 4.*•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, 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. [NOTE—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 the *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.*~~

•*Acceptance Table 2.*•2

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%

•(Official April 1, 2006)•2

BRIEFING

Nitrofurantoin Capsules, *USP 28* page 1381—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-2

Change to read:

Dissolution ⟨711⟩—

TEST 1 (where it is labeled as containing Nitrofurantoin macrocrystals)—

Medium: pH 7.2 (±0.05) phosphate buffer; 900 mL.

Harmonization

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 *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 point conforms to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩;~~

•*Acceptance Table 2,*•
and the percentages dissolved at the 3- and 8-hour points conform to the criteria for the final test time in ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩.~~

•*Acceptance Table 2.*•

Time (hours)	Amount dissolved
1	between 20% and 60%
3	not less than 45%
8	not less than 60%

TEST 2 (where it is 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 for 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 L, 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*).

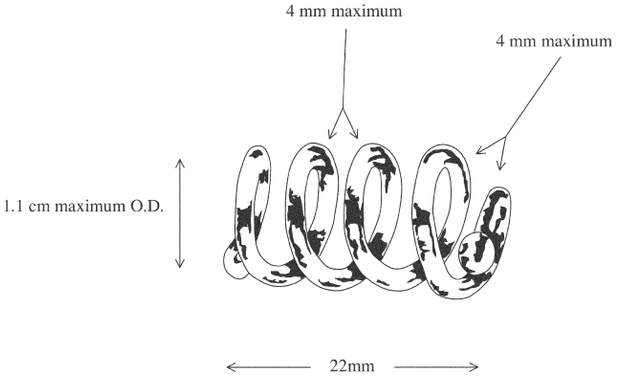


Fig. 1. Sinker.

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, suitably 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 of $C_8H_6N_4O_5$ dissolved at the specified times conform to the accompanying *Acceptance Table.*

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%

Acceptance Table

Level	Number Tested	Criteria
L_1	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.
L_2	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. 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 are less than the stated amount at the final test time.

•(Official April 1, 2006)•

BRIEFING

Omeprazole Delayed-Release Capsules, *USP 28* page 1417 and page 143 of *PF* 30(1) [Jan.–Feb. 2004]—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-3

Change to read:

Labeling—When more than one ~~*Drug Release* test~~

•*Dissolution Test*•2
is given, the labeling states the ~~*Drug Release* test~~

•*Dissolution Test*•2
used only if *Test 1* is not used.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release**~~

•**Dissolution** ⟨711⟩—•2
TEST 1~~, METHOD A ⟨724⟩~~—

••2
ACID RESISTANCE STAGE—
Medium: 0.1 N hydrochloric acid; 500 mL.
Apparatus 2: 100 rpm.
Time: 2 hours.
pH 7.6 Phosphate buffer, Mobile phase, and *Chromatographic system*—Proceed as directed for *Buffer stage.*
Standard solution—Transfer about 50 mg of USP Omeprazole RS, accurately weighed, to a 250-mL volumetric flask, dissolve in 50 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix. Transfer 10.0 mL of this solution into a 100-mL volumetric flask, add 20 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix.
Test solution—After 2 hours, filter the *Dissolution Medium* containing the pellets through a sieve with an aperture of not more than 0.2 mm. Collect the pellets on the sieve, and rinse them with water. Using approximately 60 mL of 0.01 M sodium borate solution, carefully transfer the pellets quantitatively to a 100-mL volumetric flask. Sonicate for about 20 minutes until the pellets are broken up. Add 20 mL of alcohol to the flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropriate amount of this solution with 0.01 M sodium borate solution to obtain a solution having a concentration of about 0.02 mg per mL.

•At level L_1, test 6 units. Test 6 additional units at level L_2, and at level L_3, an additional 12 units are tested. Continue testing through the three levels unless the results conform at either L_1 or L_2.•2
Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in the *Medium* by the formula:

$$T - CD(r_U / r_S),$$

in which T is the labeled quantity, in mg, of omeprazole in the capsule; C is the concentration, in mg per mL, of USP Omeprazole RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from the *Test solution* and the *Standard solution,* respectively.
Tolerances—Level L_1: no individual value exceeds 15% of omeprazole dissolved. Level L_2: the average of 12 units is not more than 20% of omeprazole dissolved, and no individual unit is greater than 35% of omeprazole dissolved. Level L_3: the average of 24 units is not more than 20% of omeprazole dissolved, not more than 2 units are greater than 35% of omeprazole dissolved, and no individual unit is greater than 45% of omeprazole dissolved.
BUFFER STAGE—
Medium: pH 6.8 phosphate buffer, 900 mL.
Proceed as directed for *Acid resistance stage* with a new set of capsules from the same batch. After 2 hours, add 400 mL of 0.235 M dibasic sodium phosphate to the 500 mL of 0.1 N hydrochloric acid medium in the vessel. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Apparatus 2: 100 rpm.
At the end of 30 minutes, determine the amount of $C_{17}H_{19}N_3O_3S$ dissolved in pH 6.8 phosphate buffer by employing the following method.
pH 10.4, 0.235 M Dibasic sodium phosphate—Dissolve 33.36 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with 2 N sodium hydroxide to a pH of 10.4 ± 0.1.
pH 6.8 Phosphate buffer—Add 400 mL of 0.1 N hydrochloric acid to 320 mL of *pH 10.4, 0.235 M Dibasic sodium phosphate,* and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.
pH 7.6 Phosphate buffer—Dissolve 0.718 g of monobasic sodium phosphate and 4.49 g of dibasic sodium phosphate in 1000 mL of water. Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 7.6 ± 0.1. Dilute 250 mL of this solution with water to 1000 mL.
Mobile phase—Transfer 340 mL of acetonitrile to a 1000-mL volumetric flask, dilute with *pH 7.6 Phosphate buffer* to volume, and pass through a membrane filter having a 0.5-µm or finer porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard solution 1 (for Capsules labeled 10 mg)—Dissolve an accurately weighed quantity of USP Omeprazole RS in alcohol to obtain a solution having a known concentration of about 2 mg per mL. Dilute with *pH 6.8 Phosphate buffer* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.01 mg per mL. Immediately add 2 mL of 0.25 M sodium hydroxide to 10 mL of this solution, and mix. [NOTE—Do not allow the solution to stand before adding the sodium hydroxide solution.]
Standard solution 2 (for Capsules labeled 20 mg and 40 mg)—Proceed as directed for *Standard solution 1,* except to obtain a solution having a known concentration of about 0.02 mg per mL before mixing with 2 mL of 0.25 M sodium hydroxide.
Test solution 1 (for Capsules containing 10 mg and 20 mg)—Immediately transfer 5.0 mL of the solution under test to a test tube containing 1.0 mL of 0.25 M sodium hydroxide. Mix well, and pass through a membrane filter having a 1.2-µm or finer porosity. Protect from light.
Test solution 2 (for Capsules labeled 40 mg)—Immediately transfer 5.0 mL of the solution under test to a test tube containing 2.0 mL of 0.25 M sodium hydroxide and 5 mL of *pH 6.8 Phosphate buffer.* Mix well, and pass through a membrane filter having a 1.2-µm or finer porosity. Protect from light.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 12.5-cm analytical column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the appropriate *Standard solution,* and record the peak responses as directed for *Procedure:* 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 20 µL) of the appropriate *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved by the formula:

$$VCD(r_U/r_S),$$

in which V is the volume of *Medium* in each vessel; C is the concentration, in mg per mL, of USP Omeprazole RS in the appropriate *Standard solution; D* is the dilution factor used in preparing the appropriate *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from the appropriate *Test solution* and the *Standard solution,* respectively.

Tolerances—For Capsules labeled 10 and 20 mg, not less than 75% *(Q)* of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 30 minutes. For Capsules labeled 40 mg, not less than 70% (*Q*) of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 30 minutes.

•The requirements are met if the quantities dissolved from the product conform to *Acceptance Table 1.*•2

TEST 2 —⟨~~711~~⟩

••2

If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2

ACID RESISTANCE STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 2 hours.

Procedure—After 2 hours, remove each sample from the basket, and quantitatively transfer into separate volumetric flasks to obtain a solution having a final concentration of about 0.2 mg per mL. Proceed as directed for the *Assay preparation* in the *Assay,* starting with "Add about 50 mL of *Diluent*". Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in the *Medium* by the formula:

$$T - CD(r_U/r_S)$$

in which T is the assayed quantity, in mg, of omeprazole in the capsule; C is the concentration, in mg per mL, of USP Omeprazole RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from *Test solution* and *Standard solution,* respectively.

Tolerances—It complies with the following *Acceptance Table:*

Acceptance Table

Level	Criterion
L_1	the average of the 6 units is not more than 10% of omeprazole dissolved
L_2	the average of the 12 units is not more than 10% of omeprazole dissolved
L_3	the average of the 24 units is not more than 10% of omeprazole dissolved

BUFFER STAGE—

Medium: 0.05 M pH 6.8 phosphate buffer; 900 mL (see *Reagents, Indicators, and Solutions*).

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Proceed as directed for *Acid resistance stage* with a new set of capsules from the same batch. After 2 hours, replace the acid medium with the buffer medium and continue the test for 45 more minutes. Determine the amount of $C_{17}H_{19}N_3O_3S$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 305 nm on portions of the solutions under test passed through a 0.2-µm nylon filter, in comparison with a Standard solution having a known concentration of USP Omeprazole RS in the same *Medium.*

Tolerances—It complies with ~~the *Acceptance Table*~~

•*Acceptance Table 1*•2

under *Dissolution* ⟨711⟩. Not less than 75% *(Q)* of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 45 minutes.

•(Official April 1, 2006)•2

BRIEFING

Oxprenolol Hydrochloride Extended-Release Tablets, *USP 28* page 1431—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-4

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•2

Acid medium: 0.1 N hydrochloric acid; 900 mL.

Dissolution medium: simulated intestinal fluid TS (without enzyme); 900 mL.

Apparatus 1: 100 rpm.

Times: 1 hour in *Acid medium;* 1, 3, and 7 hours in *Dissolution medium*.

Procedure—Determine the amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorption at about 272 nm of the first solution under test, suitably diluted with *Acid medium*, in comparison with a Standard solution having a known concentration of USP Oxprenolol Hydrochloride RS in the same medium. Promptly transfer the basket containing the Tablet to *Dissolution medium*. After 1, 3, and 7 hours, respectively, remove 9.0 mL of the test solution and determine the amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorption at about 272 nm of the solution under test, suitably diluted with *Dissolution medium*, in comparison with a Standard solution having a known concentration of USP Oxprenolol Hydrochloride RS in the same medium. [NOTE—Replace the aliquots withdrawn for analysis with fresh portions of *Dissolution medium*.]

Tolerances—The percentages of the labeled amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1, in *Acid medium*	between 15% and 45%
1, in *Dissolution medium*	between 30% and 60%
3, in *Dissolution medium*	between 50% and 80%
7, in *Dissolution medium*	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Oxtriphylline Extended-Release Tablets, *USP 28* page 1434—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-16

Change to read:

Labeling—Label the Tablets to state both the content of oxtriphylline and the content of anhydrous theophylline.

•The labeling indicates the *Dissolution Test* with which the product complies.•2

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

TEST 1 (for products labeled as 400-mg tablets)—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1*. Proceed as directed for *Method B* under *Delayed-Release Articles—General Drug Release Standard, except to use Acceptance Table 1* under *Extended-Release Articles—General Drug Release Standard/.~~

•USP *Dissolution Test 1.* Proceed as directed for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

pH 7.5 Buffer—Transfer 27.22 g of monobasic potassium phosphate to a 4-L volumetric flask, add 1 L of water and 816 mL of 0.2 N sodium hydroxide, and dilute with water to about 3800 mL. Adjust with 0.2 N sodium hydroxide or phosphoric acid to a pH of 7.5, and dilute with water to volume.

Medium: 0.1 N hydrochloric acid for the first hour, then *pH 7.5 Buffer*; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Determine the amount of $C_{12}H_{21}N_5O_3$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 248 nm on filtered portions of the solution under test, diluted with *Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Oxtriphylline RS in the same *Medium*.

Times and *Tolerances*—

Time (hours)	Amount dissolved
1	between 5% and 30%
3	between 50% and 70%
5	between 65% and 85%
7	not less than 75%

TEST 2 (for products labeled as 600-mg tablets)— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1*. Proceed as directed for *Method B* under *Delayed-Release Articles—General Drug Release Standard, except to use Acceptance Table 1* under *Extended-Release Articles—General Drug Release Standard/.~~

•USP *Dissolution Test 2.* Proceed as directed for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

pH 7.5 Buffer, Apparatus, Medium, and *Procedure*—Proceed as directed for *Test 1.*

Times and *Tolerances*—

Time (hours)	Amount dissolved
1	between 15% and 40%
3	between 50% and 70%
7	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Pentoxifylline Extended-Release Tablets, *USP 28* page 1512—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-17

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Harmonization

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•[2]

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•[2]
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 *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.*~~

•*Acceptance Table 2.*•[2]

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.*~~

•USP *Dissolution Test 2.*•[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 78%
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.*~~

•USP *Dissolution Test 3.*•[2]
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.*~~

•USP *Dissolution Test 4.*•[2]
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.*~~

•USP *Dissolution Test 5.*•[2]
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.*~~

•USP *Dissolution Test 6.*•[2]
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.*~~

•USP *Dissolution Test 7.*•[2]
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.*~~

•USP *Dissolution Test 8.*•$_2$
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.*~~

•USP *Dissolution Test 9.*•$_2$
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.*~~

•USP *Dissolution Test 10.*•$_2$
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%

•(Official April 1, 2006)•$_2$

BRIEFING

Phenylpropanolamine Hydrochloride Extended-Release Capsules, *USP 28* page 1545—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-5

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•USP *Dissolution Test*•$_2$
with which the product complies.

•(Official April 1, 2006)•$_2$

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•$_2$
TEST 1— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•$_2$
Medium: water; 1000 mL.
Apparatus 1: 100 rpm.
Times: 3, 6, and 12 hours.
Determine the amount of $C_9H_{13}NO \cdot HCl$ dissolved by employing the following method.
Solvent A—Dissolve 1.9 g of sodium 1-hexanesulfonate in 700 mL of water, add 50 mL of 1 M monobasic sodium phosphate and 20 mL of 0.25 N triethylammonium phosphate (prepared by mixing 500 mL of a solution containing 25.3 g of triethylamine and 500 mL of a solution containing 9.6 g of phosphoric acid), and mix. Dilute with water to 1 L, and mix.
Mobile phase—Prepare a filtered and degassed mixture of *Solvent A* and methanol (100 : 82). Make adjustments if necessary (see *System Suitablity* under *Chromatography* ⟨621⟩).
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 L1. The flow rate

is about 1.5 mL per minute. Chromatograph replicate injections of a Standard solution, and record the peak 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 2%.

Procedure—Inject an accurately measured volume (about 50 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 $C_9H_{13}NO \cdot HCl$ dissolved by comparison with a Standard solution having a known concentration of USP Phenylpropanolamine Hydrochloride RS in the same medium and similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_9H_{13}NO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2*•$_2$

Time (hours)	Amount dissolved
3	between 15% and 45%
6	between 40% and 70%
12	not less than 70%

•(Official April 1, 2006)•$_2$

BRIEFING

Phenylpropanolamine Hydrochloride Extended-Release Tablets, *USP 28* page 1547—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-6

Change to read:

Labeling—The labeling states the in vitro ~~*Drug release*~~

•*Dissolution*•$_2$
test conditions of *Times* and *Tolerances,* as directed under ~~*Drug release*~~

•*Dissolution.*•$_2$

•(Official April 1, 2006)•$_2$

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•$_2$
Medium: water; 1000 mL.
Apparatus 1: 100 rpm.
Times and *Tolerances:* as specified in the *Labeling*; use ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$
Determine the amount of $C_9H_{13}NO \cdot HCl$ dissolved, employing the following method.

Solvent A, *Mobile phase*, *Chromatographic system*, and *Procedure*—Proceed as directed in *Test 1* for ~~*Drug release*~~

•*Dissolution*•$_2$
under *Phenylpropanolamine Hydrochloride Extended-Release Capsules*.

•(Official April 1, 2006)•$_2$

BRIEFING

Pilocarpine Ocular System, *USP 28* page 1560—See briefing under *Aspirin Delayed-Release Capsules*.

(BPC: W. Brown) RTS—42035-7

Change to read:

Drug release pattern—Place each of the Ocular Systems in suitable porous holders made of an inert material, and suspend each from a nickel wire. To the upper end of the wire attach a tag identifying the specimen. Put each assembly into a test tube containing 27.0 mL of saline TS so that the system lies at the bottom of the tube and the identifying tag extends from the open top of the tube. Put the tubes into a horizontally reciprocating shaker in which the temperature is maintained at $37 \pm 0.5^\circ$. Agitate the tubes with a horizontal amplitude of about 4 cm and a frequency of about 35 cycles per minute. At 7, 24, 48, 72, 96, and 168 hours, remove the assemblies from their tubes, and each time replace them in similar tubes containing 27.0 mL of fresh saline TS. Determine the amount of pilocarpine in solution in each tube, after adjusting the volume to 27.0 mL to make up for any evaporative losses, by measuring the UV absorbance in 1-cm cells at the wavelength of maximum absorbance at about 215 nm, with a suitable spectrophotometer, against saline TS as the blank. Concomitantly measure the absorbance of a Standard solution of USP Pilocarpine Hydrochloride RS having a known concentration of about 20 µg in each mL of saline TS. Calculate the quantity, in µg, of $C_{11}H_{16}N_2O_2$ in each solution taken by the formula:

$$(208.26 / 244.72)(A_U / A_S)27C,$$

in which 208.26 and 244.72 are the molecular weights of pilocarpine and pilocarpine hydrochloride, respectively; A_U and A_S are the absorbances of the test solution and the Standard solution, respectively; and C is the concentration, in µg per mL, of USP Pilocarpine Hydrochloride RS in the Standard solution. Calculate the amount of pilocarpine released in 168 hours by adding the pilocarpine content of each set of tubes collected over 168 hours.

Tolerances—The amount of $C_{11}H_{16}N_2O_2$ from each Ocular System released during the total 0 to 168 hours tested conforms to ~~*Acceptance Table 4*~~

•*Acceptance Table 1*•$_2$

under *Drug Release* ⟨724⟩. The drug release range for this time period is not less than 80.0% and not more than 120.0% of the labeled release pattern.

•(Official April 1, 2006)•2

BRIEFING

Procainamide Hydrochloride Extended-Release Tablets, *USP 28* page 1626—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-24

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 50 rpm.
Times: 1, 4, and 6 hours.
Procedure—Determine the amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 224 nm, using filtered portions of the solution under test, diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Procainamide Hydrochloride RS in the same *Medium*.
Tolerances—The percentage of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved ~~is within the range stated at each of the following times~~

•at the times specified conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
6	not less than 75%

TEST 2—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2
Medium: Proceed as directed for *Method B* under ~~*Delayed-Release (Enteric-Coated) Articles.*~~

•*Delayed-Release Dosage Forms.*•2
ACID STAGE—0.1 N hydrochloric acid; 900 mL for 1 hour.
BUFFER STAGE—0.05 M phosphate buffer, pH 7.5; 900 mL (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*) for not less than 8 hours.
Apparatus 2: 50 rpm, with sinkers.
Times: 1, 4, and 8 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1.*
Tolerances—~~Proceed as directed for *Interpretation* under *Method A,* except to employ the criteria in *Acceptance Table 1* instead of *Acceptance Table 3.*~~

••2
The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 3.*~~

•USP *Dissolution Test 3.*•2
Medium: Proceed as directed under *Test 2.*
Apparatus 2: 50 rpm, with sinkers.
Times: 1, 3, 6, and 8 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1.*
Tolerances—~~Proceed as directed for *Interpretation* under *Method A,* except to employ the criteria in *Acceptance Table 1* instead of *Acceptance Table 3.*~~

••2
The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 25% and 50%
3	between 40% and 75%
6	between 65% and 90%
8	not less than 80%

TEST 4—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 4.*~~

•USP *Dissolution Test 4.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 50 rpm.
Times: 1, 2, 4, 8, and 14 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1.*
Tolerances—~~Proceed as directed for *Interpretation* under *Method A,* except to employ the criteria in *Acceptance Table 1.*~~

••2

Harmonization

The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 30%
2	between 25% and 45%
4	between 45% and 75%
8	between 70% and 90%
14	not less than 80%

TEST 5—If the product complies with this test the labeling indicates that the product meets ~~USP *Drug Release Test 5.*~~

•USP *Dissolution Test 5.*•2
Medium: Proceed as directed for *Method B* under ~~*Delayed-Release (Enteric-Coated) Articles.*~~

•*Delayed-Release Dosage Forms.*•2
ACID STAGE—0.1 N hydrochloric acid; 1000 mL for 1 hour.
BUFFER STAGE—0.05 M phosphate buffer, pH 7.5; 1000 mL (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*) for not less than 8 hours.
Apparatus 2: 50 rpm, with sinkers.
Times: 1, 4, 6, and 8 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1*.
Tolerances—Proceed as directed for *Tolerances* in *Test 2*.
FOR 500 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 45%
4	between 55% and 75%
6	not less than 65%
8	not less than 75%

FOR 750 AND 1000 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
6	between 70% and 90%
8	not less than 75%

TEST 6—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 6.*~~

•USP *Dissolution Test 6.*•2
Medium: Proceed as directed for *Test 2*.
Apparatus 2: 50 rpm.
Times: 1, 4, and 8 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1*.
Tolerances—Proceed as directed for *Tolerances* in *Test 2*.
FOR 250 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
8	not less than 80%

FOR 500 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
8	not less than 85%

FOR 750 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
8	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 8.*~~

•USP *Dissolution Test 8.*•2
Medium: Proceed as directed for *Method B* under ~~*Delayed-Release (Enteric-Coated) Articles.*~~

•*Delayed-Release Dosage Forms.*•2
ACID STAGE—0.1 N hydrochloric acid; 900 mL for 1 hour.
BUFFER STAGE—0.05 M phosphate buffer, pH 7.5; 900 mL (see *Buffer Solutions* under *Reagents*, *Indicators, and Solutions*) for not less than 8 hours.
Apparatus 2: 50 rpm, with sinkers.
Times: 1, 4, 6, and 8 hours.
Procedure—Proceed as directed for *Procedure* in *Test 1*.
Tolerances—Proceed as directed for *Tolerances* in *Test 2*.

Time (hours)	Amount dissolved
1	between 33% and 50%
4	between 70% and 85%
6	not less than 80%
8	not less than 85%

•(Official April 1, 2006)•2

BRIEFING

Progesterone Intrauterine Contraceptive System, *USP 28* page 1636—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-25

Change to read:

Drug release pattern—Remove the attached sutures from 10 Systems, and secure each system to a corrosion-resistant wire of sufficient length such that the systems are completely immersed during the shaking operation but do not touch the bottoms of the flasks. Suspend each system by the attached wire from the arm of a mechanical shaker designed to travel 2.5 cm in each direction in a

vertically reciprocating cycle, at a speed of 2.5 cycles per second, so that each system is immersed in a separate 250-mL volumetric flask containing 230 mL of water, pre-equilibrated to 60 ± 0.1°. Immerse the volumetric flasks in an insulated constant-temperature water bath, maintained at 60 ± 0.1° and having a suitable means of maintaining the water level, so that the water level of the bath is above the water level in the flasks. Employ a rack or other suitable means of support for the flasks in the water bath.

Operate the shaker under the conditions described above for 23.5 hours, then remove the flasks and the systems from the bath. Remove the systems from the flasks, and immerse each system in a different flask containing 230 mL of water, pre-equilibrated to 60 ± 0.1°, and immerse these flasks in the water bath. Repeat this shaking operation daily for 12 days, using different flasks each day.

Determine the quantity of progesterone in the solutions from each of the 12 days of testing as follows. Immediately add 15 mL of methanol to each solution, allow to cool to room temperature, dilute with water to volume, and mix. Concomitantly determine the UV absorbances of each test solution and of a solution of USP Progesterone RS in the same medium, having a known concentration of about 7 µg per mL, in 2-cm cells at the wavelength of maximum absorbance at about 248 nm, with a suitable spectrophotometer, against a blank of water and methanol (47 : 3). Calculate the progesterone release rate, in mg per day, in the solutions taken by the formula:

$$(A_U / A_S)(24 / 23.5)0.25C,$$

in which A_U and A_S are the absorbances of the test solution and the Standard solution, respectively; and C is the concentration, in µg per mL, of USP Progesterone RS in the Standard solution. For the time points specified, the drug-release pattern conforms to ~~*Acceptance Table 4*~~

•*Acceptance Table 1*•2
under *Drug Release* ⟨724⟩.

Day	Release Rate (mg per day)
6	1.05–1.45
9	0.95–1.35
12	0.90–1.30

•(Official April 1, 2006)•2

BRIEFING

Propranolol Hydrochloride Extended-Release Capsules, *USP 28* page 1659—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-26

Change to read:

Labeling—The labeling states the ~~*Drug Release Test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2

pH 1.2 Buffer solution—Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, dilute with water to 1 L, and mix.

pH 6.8 Buffer solution—Dissolve 21.72 g of anhydrous dibasic sodium phosphate and 4.94 g of citric acid monohydrate in water, dilute with water to 1 L, and mix.

Media—Proceed as directed under *Method B* for ~~*Delayed release (Enteric-coated) Articles*~~

•*Delayed-Release Dosage Forms,*•2
using 900 mL of *pH 1.2 Buffer solution* during the *Acid stage,* run for 1.5 hours, and use the acceptance criteria given under *Tolerances*. For the *Buffer stage*, use 900 mL of *pH 6.8 Buffer solution*, run for the time specified, and use the acceptance criteria given under *Tolerances*.

Apparatus 1: 100 rpm.

Times: 1.5, 4, 8, 14, and 24 hours.

Procedure—Using filtered portions of the solution under test, diluted if necessary, determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, by comparison with a Standard solution in water having a known concentration of USP Propranolol Hydrochloride RS.

Tolerances—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1.5	not more than 30%
4	between 35% and 60%
8	between 55% and 80%
14	between 70% and 95%
24	between 81% and 110%

TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2

pH 1.2 Buffer solution—Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, dilute with water to 1 L, and mix.

pH 7.5 Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate and 1.6 g of sodium hydroxide in 900 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.5, dilute with water to 1 L, and mix.

Media—Proceed as directed under *Method B* for ~~*Delayed-release (Enteric-coated) Articles—General Drug Release Standard*~~

•*Delayed-Release Dosage Forms,*•
using 900 mL of *pH 1.2 Buffer solution* during the *Acid stage,* run for 1 hour, and use the acceptance criteria given under *Tolerances*. For the *Buffer stage*, use 900 mL of *pH 7.5 Buffer solution*, run for the time specified, and use the acceptance criteria given under *Tolerances.*

Apparatus 1: 50 rpm.

Times: 1 hour, 3, 6, and 12 hours.

Procedure—Using filtered portions of the solution under test, diluted if necessary, determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, by comparison with a Standard solution in water having a known concentration of USP Propranolol Hydrochloride RS.

Tolerances—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•

Time (hours)	Amount dissolved
1	not more than 20%
3	between 20% and 45%
6	between 45% and 80%
12	not less than 80%

•(Official April 1, 2006)•

BRIEFING

Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules, *USP 28* page 1661—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-27

Change to read:

~~**Drug release** ⟨724⟩~~ —

•**Dissolution** ⟨711⟩—•
pH 1.5 Buffer solution, pH 6.8 Buffer solution, Media, and *Apparatus*—Proceed as directed in the test for ~~*Drug release*~~

•*Dissolution*•
under *Propranolol Hydrochloride Extended-Release Capsules*.

Analytical method—Determine the amounts of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) and propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved, using the following method.

Stock standard solution A—Prepare a solution of USP Propranolol Hydrochloride RS in dilute hydrochloric acid (1 in 100) having a known concentration of about 0.4 mg per mL.

Stock standard solution B—Dissolve an accurately weighed quantity of USP Hydrochlorothiazide RS in 0.25 N sodium hydroxide to obtain a solution having a concentration of about 25 mg per mL. Quantitatively dilute this solution with water to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard solution—Prepare, by combining aliquots of *Stock standard solutions*, *A* and *B*, and diluting with dilute hydrochloric acid (1 in 100), solutions bracketing the expected concentration of the samples at the various time points.

Times: 30 minutes; 1.5 hours; 4 hours; 8 hours; 14 hours; 24 hours.

Procedure—Use an automatic analyzer consisting of a liquid sampler, a proportioning pump, two UV spectrophotometers, and a manifold consisting of the components illustrated in the diagram under *Automated Methods of Analysis* ⟨16⟩. Start the sampler and conduct determinations at a rate of 30 per hour, using a ratio of about 1 : 1 for the sample to wash time. Calculate the amounts of $C_7H_8ClN_3O_4S_2$ and $C_{16}H_{21}NO_2 \cdot HCl$ dissolved by comparison with the *Standard solution.*

Tolerances (*Hydrochlorothiazide*)—Use ~~*the Acceptance Table under Dissolution* ⟨711⟩~~.

•*Acceptance Table 1.*•
Not less than 80% *(Q)* of the labeled amount of $C_7H_8ClN_3O_4S_2$ is dissolved in 30 minutes.

Tolerances (*Propranolol Hydrochloride*)—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1* under *Drug Release* ⟨724⟩~~.

•*Acceptance Table 2.*•

Time (hours)	Amount dissolved (%)
1.5	not more than 30%
4	between 35% and 60%
8	between 55% and 80%
14	between 70% and 95%
24	between 83% and 108%

•(Official April 1, 2006)•

BRIEFING

Pseudoephedrine Hydrochloride Extended-Release Capsules, *USP 28* page 1671—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-28

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•[2]
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved, employing the procedure set forth in the *Assay,* using a filtered portion of the solution under test as the *Assay preparation* in comparison with a Standard solution having a known concentration of USP Pseudoephedrine Hydrochloride RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•[2]

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•[2]

BRIEFING

Pseudoephedrine Hydrochloride Extended-Release Tablets, *USP 28* page 1673—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-13

Change to read:

Labeling—When more than one ~~*Drug Release*~~

•*Dissolution Test*•[2]
is given, the labeling states the ~~*Drug Release*~~

•*Dissolution Test*•[2]
used only if *Test 1* is not used.

•(Official April 1, 2006)•[2]

Change to read:

~~**Drug release** ⟨724⟩~~

•**Dissolution** ⟨711⟩—•[2]
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*—

•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2.*•[2]

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.*~~

•USP *Dissolution Test 3.*•[2]
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*—

•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2.*•[2]

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.*~~

•USP *Dissolution Test 2.*•[2]
Medium: 0.9% sodium chloride in water; 50 mL.
Apparatus 7

•(see *Drug Release* ⟨724⟩):•[2]

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⟩.)~~

•(see *Figure 4c* under *Drug Release* ⟨724⟩)•2 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.

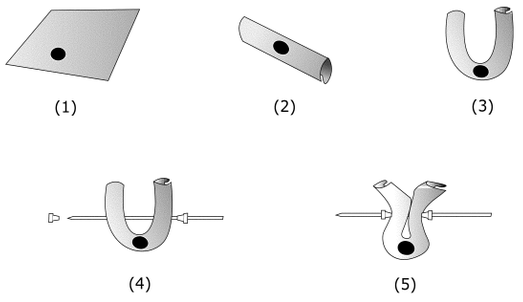


Fig. 1

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*—

•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2*.•2

Time (hours)	Amount dissolved
2	between 20% and 35%
8	between 40% and 65%
14	between 60% and 90%
24	not less than 85%

•(Official April 1, 2006)•2

BRIEFING

Quinidine Gluconate Extended-Release Tablets, *USP 28* page 1693—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-14

Change to read:

Labeling—The labeling indicates the ~~*Drug Release test*~~

•*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1*.•2

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 L 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, 2, 4, and 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 *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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 4.*•2
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.*~~

•*Acceptance Table 2.*•2

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.*~~

•USP *Dissolution Test 5.*•2
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.*~~

•*Acceptance Table 2.*•2

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

•(Official April 1, 2006)•2

* A suitable sinker is available from VanKel, www.varianinc.com, catalog number 12-3062.

BRIEFING

Quinidine Sulfate Extended-Release Tablets, *USP 28* page 1696—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-15

Change to read:

Labeling—The labeling indicates the ~~*Drug Release test*~~

•*Dissolution Test*•2
with which the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•2
TEST 1—If the product complies with the test, the labeling indicates that the product meets ~~USP *Drug Release Test 1.*~~

•USP *Dissolution Test 1.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm.
Times: 1, 4, and 12 hours.
Procedure—Using filtered portions of the solution under test, diluted with 0.1 N hydrochloric acid if necessary, determine the amount of quinidine sulfate dissolved from UV absorbances at the wavelength of maximum absorbance at about 248 nm by comparison with a Standard solution having a known concentration of USP Quinidine Sulfate RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of quinidine sulfate dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 20% and 50%
4	between 43% and 73%
12	not less than 70%

TEST 2—If the product complies with this test, the labeling indicates that the product meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm.
Times: 1, 4, and 12 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Harmonization

Time (hours)	Amount dissolved
1	between 10% and 35%
4	between 30% and 55%
12	not less than 75%

•(Official April 1, 2006)•2

BRIEFING

Sulfasalazine Delayed-Release Tablets, *USP 28* page 1834—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-36

Change to read:

~~**Drug release,** *Method B* ⟨724⟩~~—

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 120 minutes.

At the end of 120 minutes, determine the amount of $C_{18}H_{14}N_4O_5S$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, isopropanol, acetonitrile, and glacial acetic acid (22 : 11 : 7 : 0.4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Sulfasalazine RS in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 55.6 µg per mL.

Test solution—Pass about 7 mL of the solution under test through a membrane filter having a 0.45-µm porosity.

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 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time for sulfasalazine is about 7.7 minutes; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject a volume (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the peak responses. Calculate the percentage of $C_{18}H_{14}N_4O_5S$ dissolved by the formula:

$$(900C_S/LC)(r_U/r_S),$$

in which C_S is the concentration, in mg per mL, of USP Sulfasalazine RS in the *Standard solution; LC* is the label claim, in mg; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not more than 10% of the labeled amount of $C_{18}H_{14}N_4O_5S$ is dissolved in 120 minutes.

BUFFER STAGE—

Medium: pH 7.5 phosphate buffer; 900 mL.

Apparatus 1: 100 rpm.

Time: 60 minutes.

At the end of 60 minutes, determine the amount of $C_{18}H_{14}N_4O_5S$ dissolved by employing the chromatographic method as described under *Acid stage.*

Tolerances—Not less than 85% *(Q)* of the labeled amount of $C_{18}H_{14}N_4O_5S$ is dissolved in 60 minutes.

•(Official April 1, 2006)•2

BRIEFING

Theophylline Extended-Release Capsules, *USP 28* page 1897—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-21

Change to read:

Labeling—The labeling indicates whether the product is intended for dosing every 12 or 24 hours, and states with which in vitro ~~*Drug Release Test*~~

•*Dissolution Test*•2
the product complies.

•(Official April 1, 2006)•2

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•2

[NOTE—The following tests, which were assigned numbers chronologically, are placed in groups corresponding to product dosing intervals. Thus, individual tests do not necessarily appear in numerical order.]

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1— If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.* Proceed as directed for *Method B* under *Delayed-release Articles—General Drug Release Standard*, except to use *Acceptance Table 1* under *Extended-Release Articles—General Drug Release Standard*~~

•USP *Dissolution Test 1.* Proceed as directed for *Method B* under *Apparatus 1 and 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

Medium: pH 1.2 simulated gastric fluid (without pepsin) for the first hour; pH 6.0 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Procedure—Determine the amount of $C_7H_8N_4O_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 271 nm on filtered portions of the solution under test, diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Theophylline RS in the same *Medium*.

Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 3% and 15%
2	between 20% and 40%
4	between 50% and 75%
6	between 65% and 100%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•2

Medium: 4.5 phosphate buffer, prepared by dissolving 6.8 g of monobasic potassium phosphate in 750 mL of water, mix, and dilute with water to 1000 mL. Adjust the pH to 4.5 ± 0.05 using either 1 N hydrochloric acid or 1 N sodium hydroxide; 900 mL.

Apparatus 2: 75 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 30%
2	between 30% and 55%
4	between 55% and 80%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 3.*~~

•USP *Dissolution Test 3.*•2

Proceed as directed for *Method B* under ~~*Delayed-Release Articles—General Drug Release Standard*~~,except to use ~~*Acceptance Table 1*~~ under ~~*Extended-Release Articles—General Drug Release Standard*~~

•*Apparatus 1 and 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

Medium: pH 1.2 simulated gastric fluid (without pepsin) for 1 hour; pH 7.5 simulated intestinal fluid (without enzyme); 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 1% and 17%
2	between 30% and 60%
3	between 50% and 90%
4	not less than 65%
7	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 4*~~

•USP *Dissolution Test 4.*•2

Proceed as directed for *Method A* under ~~*Delayed-Release Articles—General Drug Release Standard*~~, except to use ~~*Acceptance Table 1*~~ under ~~*Extended-Release Articles—General Drug Release Standard*~~

•*Apparatus 1 and 2, Delayed-Release Dosage Forms*, except to use *Acceptance Table 2.*•2

Medium: pH 3.0 phosphate buffer, 0.05 M potassium phosphate buffer adjusted with phosphoric acid to a pH of 3.0 ± 0.05, for the first 3½ hours, followed by the addition of 5.3 M sodium hydroxide to adjust to a pH of 7.4 ± 0.05; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 13% and 38%
2	between 25% and 50%
3.5	between 37% and 65%
5	between 85% and 115%

TEST 5—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 5.*~~

•USP *Dissolution Test 5.*•2

Medium, *Apparatus*, and *Procedure*—Proceed as directed under *Test 4*.

Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 30%
3.5	between 30% and 60%
5	between 50% and 80%
7	not less than 65%
10	not less than 80%

TEST 7—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 7*~~

•USP *Dissolution Test 7.*•2

Phosphate buffer—Dissolve 40.8 g of monobasic potassium phosphate in 6 L of water, add 667 mg of octoxynol 9, mix, and adjust with dilute hydrochloric acid or sodium hydroxide to a pH of 4.5.

Medium: Phosphate buffer; 900 mL.

Apparatus 2: 50 rpm.
Procedure—Proceed as directed under *Test 1*.
Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 10% and 40%
2	between 35% and 70%
4	between 60% and 90%
8	not less than 85%

TEST 8—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 8*~~

•USP *Dissolution Test 8.*•$_2$
Medium: pH 7.5 simulated intestinal fluid (without enzyme); 900 mL.
Apparatus 1: 100 rpm.
Procedure—Proceed as directed under *Test 1*.
Times and *Tolerances*—The percentages of labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 3% and 30%
2	between 15% and 50%
4	between 45% and 80%
6	not less than 70%
8	not less than 85%

TEST 9—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 9*~~

•USP *Dissolution Test 9.*•$_2$
Medium 1: 0.1 N hydrochloric acid; 900 mL.
Medium 2: simulated intestinal fluid (without enzyme); 900 mL.
Apparatus 1: 50 rpm.
Determine the amount of theophylline dissolved at the times specified, using *Medium 1* for the first hour and *Medium 2* for the next five hours.
Procedure—Proceed as directed under *Test 1*.
Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 5% and 15%
2	between 25% and 45%
3	between 50% and 65%
4	not less than 70%
6	not less than 85%

TEST 10—If the product complies with this test, the labeling indicates that it meets ~~*USP Drug Release Test 10.*~~

•USP *Dissolution Test 10.*•$_2$
Proceed as directed for *Test 3*.
Times and *Tolerances*—

•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 6% and 27%
2	between 25% and 50%
4	between 65% and 85%
8	not less than 80%

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—
TEST 6—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 6*~~

•USP *Dissolution Test 6.*•$_2$
Medium: 0.05 M pH 6.6 phosphate buffer (see *Buffer Solutions* in the section *Reagents*, *Indicators*, *and Solutions*); 1000 mL.
Apparatus 1: 100 rpm.
Procedure—Proceed as directed under *Test 1*.
Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 5% and 15%
2	between 12% and 30%
4	between 25% and 50%
5	between 30% and 60%
8	between 55% and 75%

•(Official April 1, 2006)•$_2$

BRIEFING

Trihexyphenidyl Hydrochloride Extended-Release Capsules, *USP 28* page 1980—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-22

Change to read:

~~**Drug release** ⟨724⟩~~—

•**Dissolution** ⟨711⟩—•$_2$
Medium: water; 500 mL.
Apparatus 1: 100 rpm.
Times: 3, 6, and 12 hours.
Determine the amount of $C_{20}H_{31}NO \cdot HCl$ dissolved, using the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and triethylamine (920 : 80 : 0.2), and adjust with phosphoric acid to a pH of 4.0.

Standard preparation—Dissolve an accurately weighed quantity of USP Trihexyphenidyl Hydrochloride RS in water, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about 5 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 8.3-cm column that contains 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 for the trihexyphenidyl peak is not more than 2.8, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Dilute the *Standard preparation* and the solution under test with acetonitrile (1 : 1). Separately inject equal volumes (about 20 µL) of these solutions into the chromatograph, record the chromatograms, and measure the responses for trihexyphenidyl. Calculate the percentage of the labeled amount of $C_{20}H_{31}NO \cdot HCl$ HCl dissolved.

Tolerances—The percentages of the labeled amount of $C_{20}H_{31}NO \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 40% and 70%
12	not less than 70%

•(Official April 1, 2006)•

BRIEFING

Verapamil Hydrochloride Extended-Release Tablets, *USP 28* page 2019—See briefing under *Aspirin Delayed-Release Capsules.*

(BPC: W. Brown) RTS—42035-23

Change to read:

Labeling—The labeling indicates the ~~*Drug Release Test*~~

•*Dissolution Test*•
with which the product complies.

•(Official April 1, 2006)•

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—•

TEST 1—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 1.* Proceed as directed for *Method B* under *Delayed-Release (Enteric-Coated) Articles—General Drug Release Standard*~~

•USP *Dissolution Test 1*. Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•

Acid stage—Using 900 mL of simulated gastric fluid TS (without enzyme), conduct this stage of the test for 1 hour.

Buffer stage—Using 900 mL of simulated intestinal fluid TS (without enzyme), conduct this stage of the test for 7 hours.

Apparatus 2: 50 rpm.

Times: Acid stage—1 hour; *Buffer stage*—2, 3.5, 5, and 8 hours.

Procedure—Wrap each Tablet in a wire helix to prevent the Tablets from floating. After 1 hour in the *Acid stage*, withdraw a specimen for analysis, and carefully transfer the dosage form, including the wire helix, to a vessel containing the *Buffer stage* medium, which has been previously warmed to 37 ± 0.5°. Filter a portion of the solution under test at each time interval, using a suitable glass microfiber filter paper. [NOTE—Use only filters that have been shown not to absorb verapamil.] Dilute, if necessary, the filtered portions of the solutions under test with water at the 1-hour interval and with 0.1 N hydrochloric acid at the 2-, 3.5-, 5-, and 8-hour intervals. Determine the amounts of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm, using 0.01 N hydrochloric acid as the blank, by comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in 0.01 N hydrochloric acid.

Tolerances—The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•

FOR PRODUCTS LABELED TO CONTAIN 180 MG OR 240 MG:

Time (hours)	Amount dissolved
1	between 7% and 15%
2	between 16% and 30%
3.5	between 31% and 50%
5	between 51% and 75%
8	not less than 85%

FOR PRODUCTS LABELED TO CONTAIN 120 MG:

Time (hours)	Amount dissolved
1	between 10% and 21%
2	between 18% and 33%
3.5	between 35% and 60%
5	between 50% and 82%
8	not less than 85%

Harmonization

TEST 2—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 2.*~~

•USP *Dissolution Test 2.*•$_2$
Proceed as directed for *Test 1*, except that under *Procedure*, the Tablet is not required to be wrapped in a wire helix.
Times and *Tolerances*—

•The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to *Acceptance Table 2.*•$_2$

FOR PRODUCTS LABELED TO CONTAIN 240 MG:

Time (hours)	Amount dissolved
1	between 8% and 20%
2	between 15% and 35%
3.5	between 35% and 65%
5	between 55% and 85%
8	not less than 80%

FOR PRODUCTS LABELED TO CONTAIN 180 MG:

Time (hours)	Amount dissolved
1	between 10% and 25%
2	between 20% and 40%
3.5	between 40% and 75%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 3.*~~

•USP *Dissolution Test 3.*•$_2$
Proceed as directed for *Test 1*.
Times and *Tolerances*—

•The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to *Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 8% and 20%
2	between 15% and 35%
3.5	between 27% and 57%
5	between 45% and 75%
8	not less than 80%

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

•USP *Dissolution Test 4.*•$_2$
Phosphate buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water. Add 190 mL of 0.2 N sodium hydroxide in 400 mL of water, adjust with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1, dilute with water to 1000 mL, and mix.
Medium: Phosphate buffer solution; 50 mL.
Apparatus 7

•(see *Drug Release* ⟨724⟩:•$_2$
20 cycles per minute.

Procedure—Scrape about 2 mm × 2 mm of the coating from the side edge of the tablet under test. Glue the system to a plastic rod sample holder at the area where the color has been removed. Attach each plastic sample holder to an arm of the apparatus, which reciprocates at an amplitude of about 2 cm and 15 to 30 cycles per minute. The tablet is continuously immersed in tubes containing 50 mL of *Medium* at 37°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium.* Remove the tubes after the last test interval, and allow them to cool to room temperature. Add 2.0 mL of 1.0 M phosphoric acid to each tube, and dilute with water to 50 mL. Stir and mix each tube thoroughly. Determine the amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ 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 *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in the same *Medium.*
Times and *Tolerances*—The percentages of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
3	not more than 10%
6	between 20% and 50%
9	between 52.5% and 82.5%
14	not less than 85%

TEST 5—If the product complies with this test, the labeling indicates that it meets ~~USP *Drug Release Test 5.*~~

•USP *Dissolution Test 5.*•$_2$
Phosphate buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water. Add 190 mL of 0.2 N sodium hydroxide in 400 mL of water, adjust with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1, dilute with water to 1000 mL, and mix.
Medium: Phosphate buffer solution; 900 mL.
Apparatus 2: 50 rpm.
Procedure—Determine the amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ 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 *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in the same *Medium*.
Times and *Tolerances*—The percentages of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conform to ~~*Acceptance Table 1.*~~

•*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 2% and 12%
2	between 10% and 25%
4	between 25% and 50%
8	not less than 80%

•(Official April 1, 2006)•$_2$

Harmonization

MONOGRAPHS (NF)

BRIEFING

Butylparaben, *NF 23* page 2969 and page 1431 of *PF* 30(4) [July–Aug. 2004]. The European Pharmacopoeia, a member of the Pharmacopeial Discussion Group, is the coordinating pharmacopeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the **ADOPTION STAGE 6** draft in the harmonization process.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification A	+	+	+
Appearance of solution	+	+	+
Acidity	+	+	+
Related substances*	+	+	+
Sulphated ash	+	+	+
Assay	+	+	+

* JP will not include the system suitability requirement and consequently will not include reference solution (b).

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Characters, Identification by infrared spectrophotometry, Storage.

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

Local requirements: JP: Heavy metals (20 ppm); USP: Organic volatile impurities.

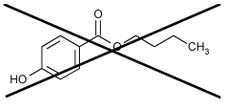
Differences between the **ADOPTION STAGE 6** document and the current *NF* monograph include the following:

(1) In the opening paragraph (the Definition)—Calculations using the dried substance are deleted, as the *Loss on drying* test is deleted. The acceptance range has been widened.
(2) *Packaging and storage*—No change.
(3) *USP Reference standards*—The reference standard for Propylparaben has been added for the *Related substances* test.
(4) *Identification*—The test for *Melting range* has been moved under *Identification*.
(5) *Color of solution*—This test is added to comply with EP standards.
(6) *Melting range*—Moved under *Identification*.
(7) *Acidity*—The EP test method has replaced the current USP method.
(8) *Loss on drying*—Deleted.
(9) *Residue on ignition*—The limits are increased to not more than 0.1% to comply with EP standards.
(10) *Organic volatile impurities*—No change.
(11) *Related substances*—This test is added to comply with EP standards. Corrections are made to the preparation of *Standard solution B* to use USP Propylparaben RS.
(12) *Assay*—The sample amount and the amount of 1 N sodium hydroxide has changed, and the heating process has changed to a specific temperature and does not include refluxing.

(EMC: J. Lane) RTS—41918-1

Change to read:

~~Butylparaben~~



~~$C_{11}H_{14}O_3$~~ ~~194.23~~
~~Benzoic acid, 4-hydroxy-, butyl ester.~~
~~Butyl *p*-hydroxybenzoate [*94-26-8*].~~

~~» Butylparaben contains not less than 99.0 percent and not more than 100.5 percent of $C_{11}H_{14}O_3$, calculated on the dried basis.~~

~~**Packaging and storage**—Preserve in well-closed containers.~~

~~**USP Reference standards** ⟨11⟩—*USP Butylparaben RS.*~~

~~**Identification,** *Infrared Absorption* ⟨197M⟩.~~

~~**Melting range** ⟨741⟩: between 68° and 72°.~~

~~**Acidity**—Heat 0.75 g in 15 mL of water at 80° for 1 minute, cool, and filter: the filtrate is neutral or acid to litmus. To 10 mL of the filtrate add 0.20 mL of 0.10 N sodium hydroxide and 2 drops of methyl red TS: the solution is yellow.~~

~~**Loss on drying** ⟨731⟩—Dry it over silica gel for 5 hours: it loses not more than 0.5% of its weight.~~

~~**Residue on ignition** ⟨281⟩: not more than 0.05%.~~

~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.~~

~~**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. 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 $C_{11}H_{14}O_3$.~~

Harmonization

▲Butylparaben

$C_{11}H_{14}O_3$ 194.23

Benzoic acid, 4-hydroxy-, butyl ester.

Butyl *p*-hydroxybenzoate [*94-26-8*].

» Butylparaben contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{14}O_3$.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—***USP Butylparaben RS*. *USP Propylparaben RS*.

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: *Melting range* ⟨741⟩: between 68° and 71°.

Color of solution—Dissolve 1 g in alcohol, dilute with alcohol to 10 mL, and mix *(Butylparaben solution)*. This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL, and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see *Color and Achromicity* ⟨631⟩).

Acidity—To 2 mL of *Butylparaben solution* prepared in the *Color of solution* test, add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition ⟨281⟩**:** not more than 0.1%, determined on 1.0 g.

Related substances—

Test solution—Prepare a solution of Butylparaben in acetone containing 10 mg per mL.

Standard solutions—Transfer 0.5 mL of the *Test solution* to a 100-mL volumetric flask, dilute with acetone to volume, and mix *(Standard solution A)*. Dissolve 10 mg, accurately weighed, of USP ~~Butylparaben~~ Propylparaben RS in 1 mL of the *Test solution,* and dilute with acetone to 10 mL *(Standard solution B)*.

Procedure—Separately apply 2 µL of the *Test solution* and 2 µL of each *Standard solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid (70 : 30 : 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 that of the principal spot in the chromatogram of *Standard solution A:* the intensity of any individual secondary spot in the chromatogram of the *Test solution* is not greater than that of the principal spot obtained in the chromatogram of *Standard solution A* (0.5%). The test is not valid unless the chromatogram obtained with *Standard solution B* shows two clearly separated principal spots.

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Assay—To about 1.000 g of Butylparaben, accurately weighed, 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 on 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 194.2 mg of $C_{11}H_{14}O_3$. ▲*NF24*

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**1**⟩ **Injections,** *USP 28* page 2201. The United States Pharmacopeia is the coordinating pharmacopeia in the efforts toward international harmonization of the specifications provided in this general test chapter. The Parenteral Products—Industrial Expert Committee in conjunction with the Pharmaceutical Discussion Group (PDG) have agreed to harmonize the text for *Determination of Volume of Injection in Containers* within the section *Volume in Container.* The text, which is being published in this issue of *PF* for information only, not for public comment, is scheduled for publication in *USP 29–NF 24* with a scheduled implementation date of **April 1, 2006.**

(PPI: J. Kelly) RTS—41973-2

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

(Official October 1, 2005)

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. ~~The contents of up to five 1- or 2-mL containers may be pooled for the measurement,~~

▲The contents of a sufficient number of containers with a nominal volume of less than or equal to 2 mL may be pooled to obtain a minimum total of 5 mL,▲*USP29* provided that a separate dry syringe assembly is used for each container. The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

(Official October 1, 2005)

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

(Official April 1, 2006)

Physical Tests and Determinations

BRIEFING

⟨**701**⟩ **Disintegration,** *USP 28* page 2411 and page 1575 of *PF* 28(5) [Sept.–Oct. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia in the efforts toward international harmonization of the specifications provided in this general test chapter. The Stage 5B text for this chapter has been signed off by the Pharmacopeial Discussion Group members. The text presented herein represents a merger of the Stage B text and the national USP text. This combined text, which is being published in this issue of *PF* for information only, not for public comment, is scheduled for publication in the *Second Interim Revision Announcement* pertaining to *USP 28–NF 23,* with a scheduled delayed implementation date of **April 1, 2006.** Earlier implementation by individual companies may be done at their discretion.

(BPC: W. Brown) RTS—42037-1

Change to read:

⟨~~701~~⟩ ~~DISINTEGRATION~~

~~This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms (see *Drug Release* ⟨724⟩). Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.~~

~~For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.~~

~~APPARATUS~~

~~The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 155 mm in height and having an inside diameter of 97 to 110 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.~~

~~**Basket-rack Assembly**— The basket-rack assembly consists of six open-ended transparent tubes, each 7.75 ± 0.25 cm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plastic plates, each 8.8 to 9.2 cm in diameter and 5 to 7 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.63 ± 0.03 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising-and-lowering device using a point on its axis.~~

~~The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.~~

~~**Disks**— The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 mm, and its center lies at a depth of 1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.~~

~~PROCEDURE~~

~~**Uncoated Tablets**— Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Plain-Coated Tablets**— Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.~~

~~**Delayed-Release (Enteric-Coated) Tablets**— Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour~~

~~of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Buccal Tablets**—Apply the test for *Uncoated Tablets.* After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Sublingual Tablets**—Apply the test for *Uncoated Tablets.* Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Hard Gelatin Capsules**—Apply the test for *Uncoated Tablets.* Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-Rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.~~

~~**Soft Gelatin Capsules**—Proceed as directed under *Hard Gelatin Capsules*.~~

•⟨701⟩ DISINTEGRATION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national *USP* text, and therefore not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.

This test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. ◆Compliance with the limits on *Disintegration* stated in the individual monographs is required except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as extended-release dosage forms or delayed-release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.◆

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than

an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plates, each 88 to 92 mm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained. The basket-rack assembly conforms to the dimensions found in *Figure 1*.

Disks—The use of disks is permitted only where specified or allowed ◆in the monograph. If specified in the individual monograph,◆ each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2 ± 0.1-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 ± 0.2 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 ± 0.1 mm, and its bottom edges lie at a depth of 1.6 ± 0.1 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified ◆in the individual monograph◆, add a disk to each tube, and operate the apparatus as directed under *Procedure*. The disks conform to dimensions found in *Figure 1*.[1]

[1] The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimension given in this chapter.

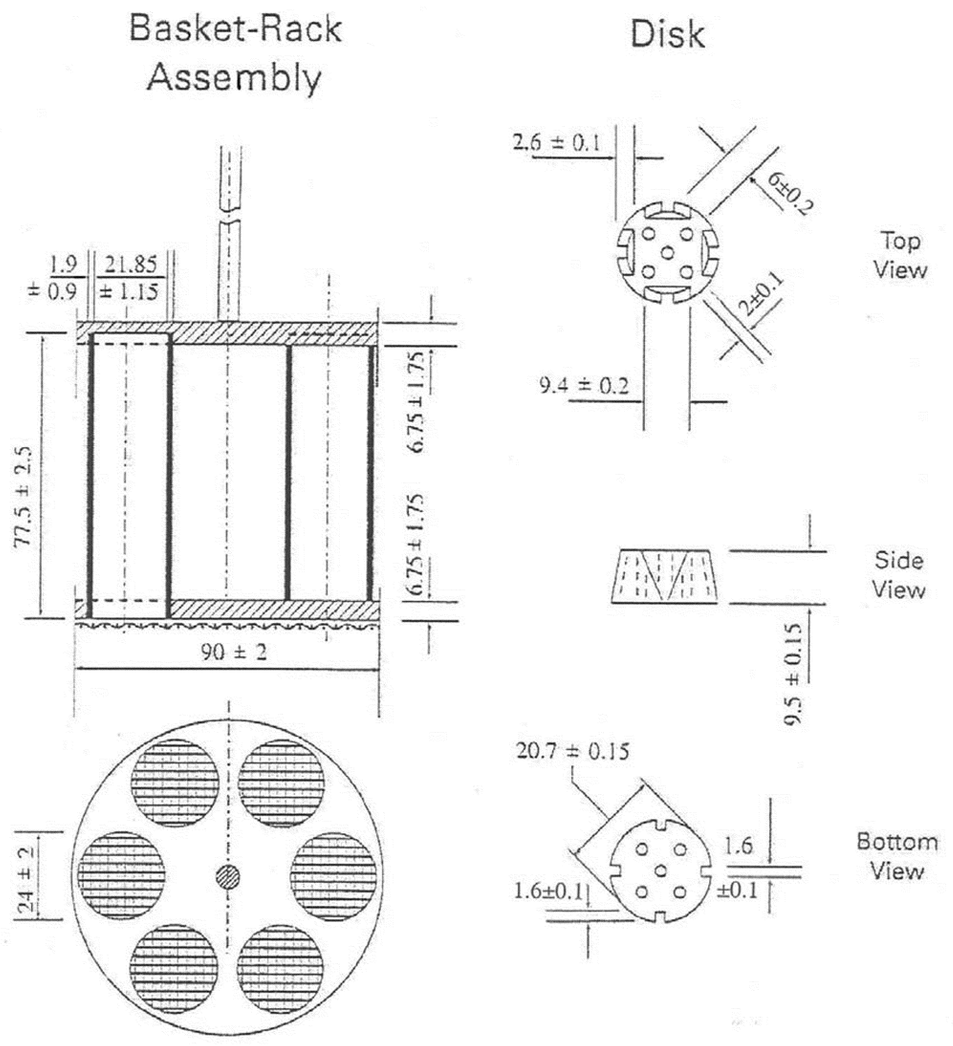


Fig. 1. Disintegration apparatus. (All dimensions are expressed in mm.)

PROCEDURE

◆**Uncoated Tablets**—◆Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus, using ◆water or◆ the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of the time limit specified ◆in the monograph,◆ lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested are disintegrated.

◆**Plain-Coated Tablets**—Apply the test for *Uncoated Tablets,* operating the apparatus for the time specified in the individual monograph.

Delayed-Release (Enteric-Coated) Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at $37 \pm 2^\circ$ as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at $37 \pm 2^\circ$ as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets.* At the end of the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-Rack Assembly,* to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.◆ ●2

(Official April 1, 2006)

BRIEFING

⟨**711**⟩ **Dissolution,** *USP 28* page 2412 and page 234 of *PF* 30(1) [Jan.–Feb. 2004]. The United States Pharmacopeia is the coordinating pharmacopeia in the efforts toward interntional harmonization of the specifications provided in this general test chapter. The Stage 5B text for this chapter has been signed off by the Pharmacopeial Discussion Group members. The text presented herein represents a merger of the Stage B text and the national USP text. This combined text, which is being published in this issue of *PF* for information only, not for public comment, is scheduled for publication in the *Second Interim Revision Announcement* with a scheduled implementation date of **April 1, 2006.** Earlier implementation by individual companies may be done at their discretion.

(BPC: W. Brown) RTS—42036-1

Change to read:

⟨~~711~~⟩ ~~DISSOLUTION~~

~~This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-Release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.~~

~~**USP Reference Standards** ⟨11⟩ *USP Prednisone Tablets RS* (*Dissolution Calibrator, Disintegrating*). *USP Salicylic Acid Tablets RS* (*Dissolution Calibrator, Nondisintegrating*).~~

Apparatus 1— The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. 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 smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 L, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 L, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation[2]. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ± 4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in *Figure 1*. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 µm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

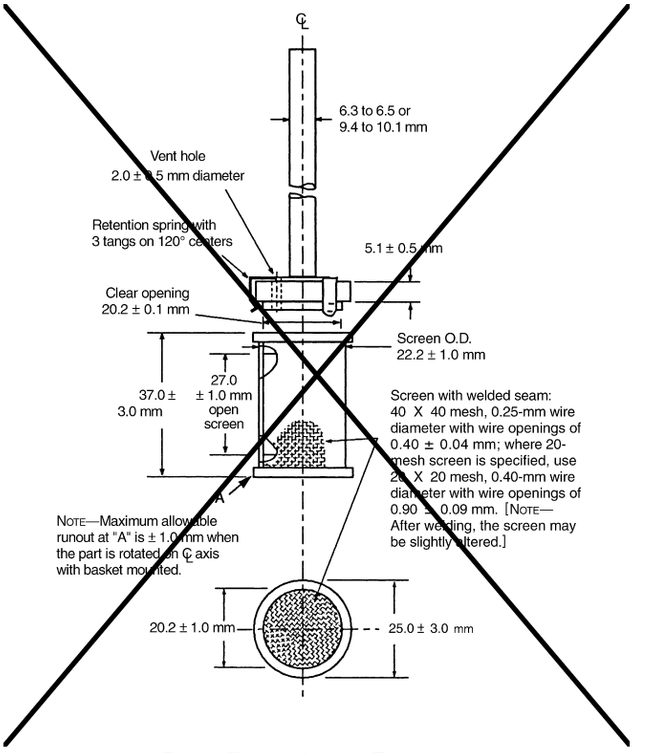


Fig. 1. Basket Stirring Element

Apparatus 2— Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in *Figure 2*. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

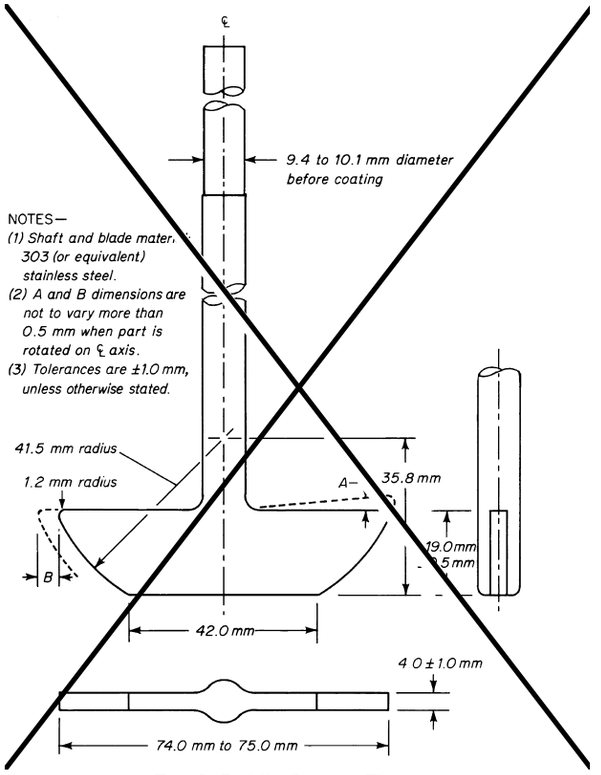


Fig. 2. Paddle Stirring Element

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type* and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type,* according to the operating 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—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ± 2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* (± 1%) in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37°, or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph[4]. Repeat the test with additional dosage form units.

If automated equipment is used for sampling and the apparatus is modified, validation of the modified apparatus is needed to show that there is no change in the agitation characteristics of the test.

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.

Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets—Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed under *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets*. Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of the active ingredient dissolved in the pooled sample.

Interpretation—

Unit Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying *Acceptance Table*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; the 5%, 15%, and 25% values in the *Acceptance Table* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q − 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q − 15%, and no unit is less than Q − 25%.

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

Harmonization

~~*Pooled Sample*~~ ~~Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.~~

~~**Acceptance Table for a Pooled Sample**~~

~~Stage~~	~~Number Tested~~	~~Acceptance Criteria~~
~~S_1~~	~~6~~	~~Average amount dissolved is not less than Q + 10%.~~
~~S_2~~	~~6~~	~~Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.~~
~~S_3~~	~~12~~	~~Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.~~

•⟨711⟩ DISSOLUTION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the European Pharmacopoeia or the Japanese Pharmacopoeia may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.

This test is provided to determine compliance with the dissolution requirements ◆where stated in the individual monograph◆ for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. ◆Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for *Delayed-Release Dosage Forms* is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

USP Reference Standards ⟨11⟩—*USP Chlorpheniramine Maleate Extended-Release Tablets RS (Drug Release Calibrator, Single Unit). USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS. (Dissolution Calibrator, Nondisintegrating).*◆

APPARATUS

Apparatus 1 (Basket Apparatus)

The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at $37 \pm 0.5^\circ$ during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due

[1] The materials should not sorb, react, or interfere with the specimen being tested.

to the smoothly rotating stirring element. An apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and ◆with one of the following dimensions and capacities: for a nominal◆ capacity of 1 L, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; ◆for a nominal capacity of 2 L, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm◆. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the specified rate ◆given in the individual monograph,◆ within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316, or other inert material, to the specifications shown in *Figure 1.* A basket having a gold coating of about 0.0001 inch (2.5 μm) thick may be used. A dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

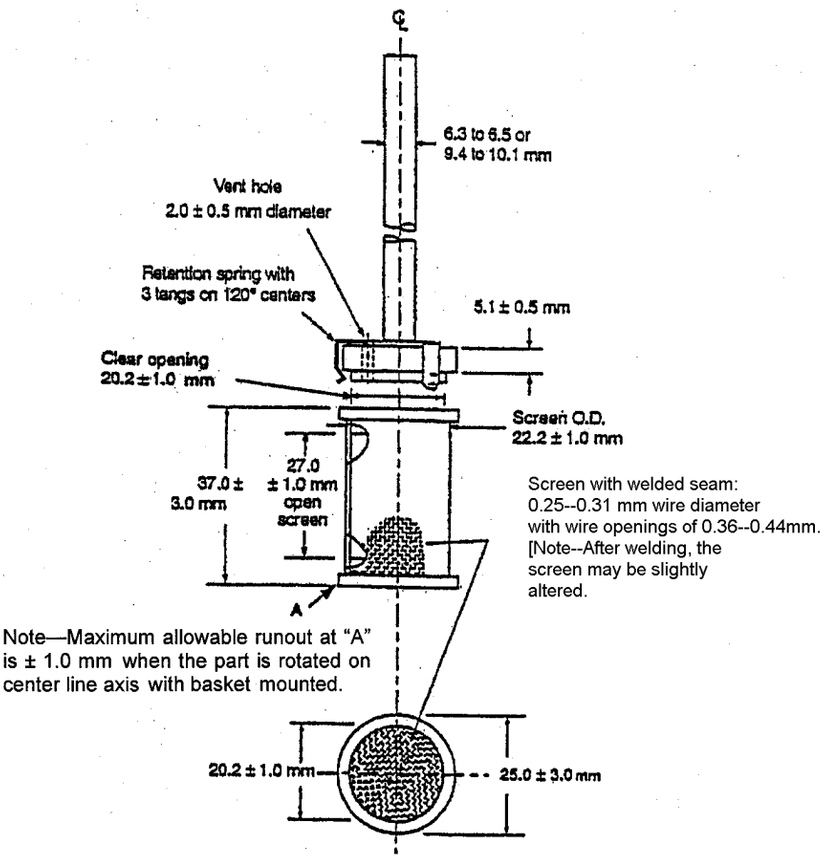


Fig. 1. Basket Stirring Element

Apparatus 2 (Paddle Apparatus)

Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in *Figure 2*. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in *Figure 2a*. Other validated sinker devices may be used.

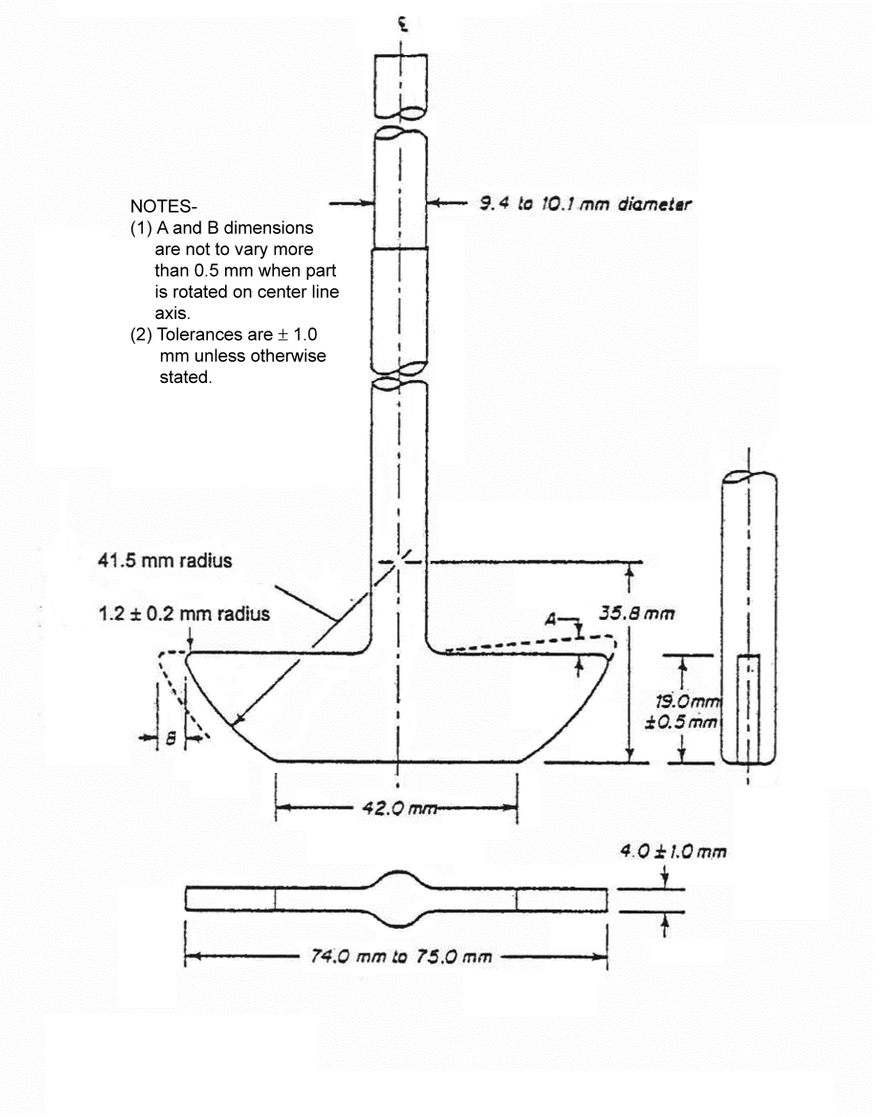


Fig. 2. Paddle Stirring Element

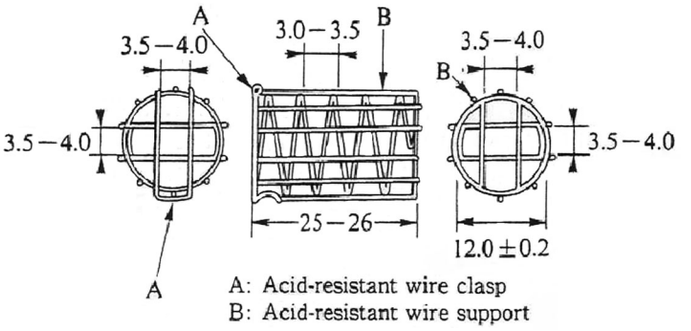


Fig. 2a. Alternative sinker. All dimensions expressed in mm.

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), 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 $37 \pm 0.5^{\circ}$ 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 specified dip rate ◆given in the individual monograph◆ within $\pm 5\%$. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The vessels are provided with an evaporation cap that remains in place for the duration of the test. The components conform to the dimensions shown in *Figure 3* unless otherwise specified ◆in the individual monograph◆.

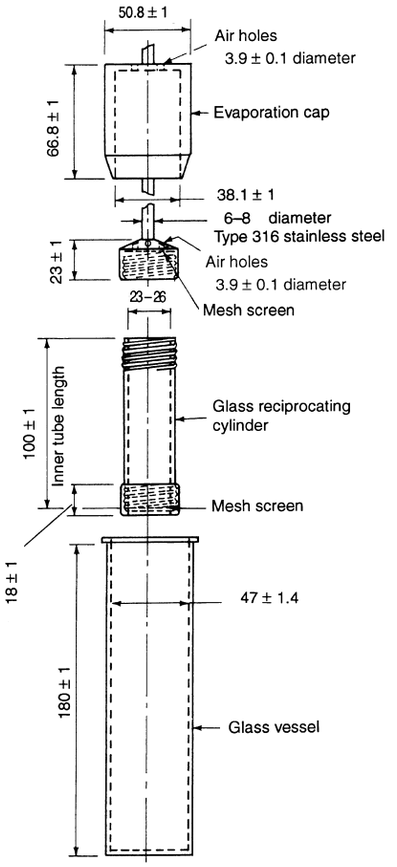


Fig. 3. Apparatus 3 (reciprocating cylinder)

Apparatus 4 (Flow-Through Cell)

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°. Use the specified cell size ◆as given in the individual monograph◆.

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 deliver a constant flow (±5% of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see *Figures 4* and *5*), 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 4* and *5*) 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°.

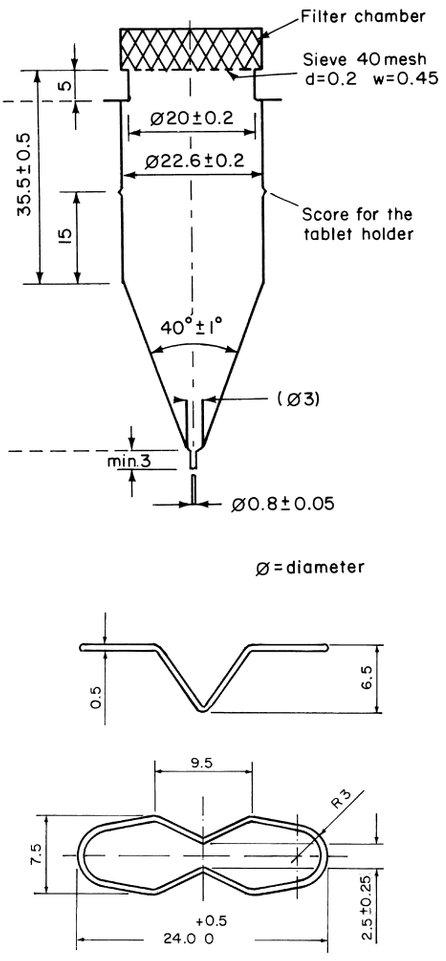


Fig. 4. Large cell for tablets and capsules (top) Tablet holder for the large cell (bottom) (All measurements are expressed in mm unless noted otherwise.)

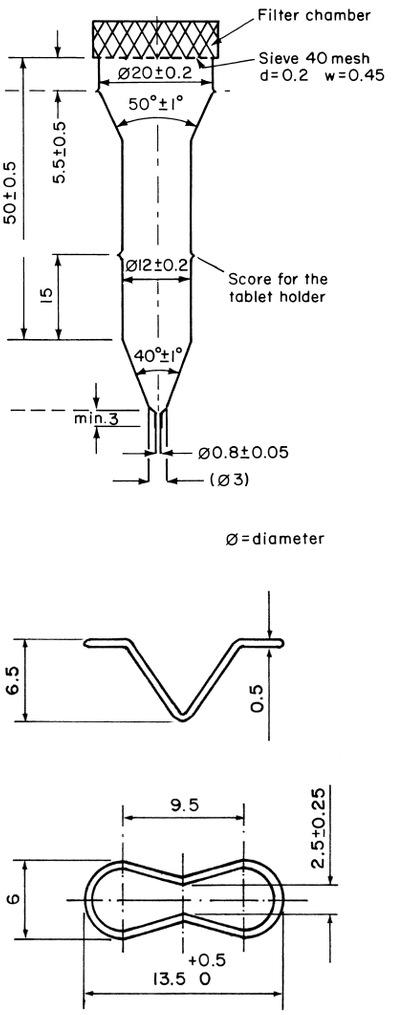


Fig. 5. Small cell for tablets and capsules (top) Tablet holder for the small cell (bottom) (All mesurements are expressed in mm unless noted otherwise.)

The apparatus uses a clamp mechanism and two O-rings to assemble the cell. 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 suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections.

APPARATUS SUITABILITY

The determination of suitability of a test assembly to perform dissolution testing must include conformance to the dimensions and tolerances of the apparatus as given above. In addition, critical test parameters that have to be monitored periodically during use include volume and temperature of the *Dissolution Medium,* rotation speed (*Apparatus 1* and *Apparatus 2*), dip rate (*Apparatus 3*), and flow rate of medium (*Apparatus 4*).

Determine the acceptable performance of the dissolution test assembly periodically. ◆The suitability for the individual apparatus is demonstrated by the *Apparatus Suitability Test*.

Apparatus Suitability Test, Apparatus 1 and 2—Individually test 1 tablet of the USP Dissolution Calibrator, Disintegrating Type and 1 tablet of USP Dissolution Calibrator, Nondisintegrating Type, according to the operating 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.

Apparatus Suitability Test, Apparatus 3—Individually test 1 tablet of the USP Drug Release Tablets (Single Unit) according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate.

Apparatus Suitability Test, Apparatus 4—[To come.]◆

PROCEDURE

Apparatus 1 and Apparatus 2

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the specified apparatus ◆given in the individual monograph,◆ assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate ◆given in the individual monograph◆. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis ◆as directed in the individual monograph◆ using a suitable assay method. [3] Repeat the test with additional dosage form units.

If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary.

[3] Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

Dissolution Medium—A suitable dissolution medium is used. Use the solvent specified ◆in the individual monograph.◆ The volume specified refers to measurements made between 20° and 25°. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH ◆given in the individual monograph.◆ [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.[4]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms.*

Time—The test-time points, generally three, are expressed in hours.

DELAYED-RELEASE DOSAGE FORMS

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

Use *Method A* or *Method B* and the apparatus specified ◆in the individual monograph.◆ All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

Method A—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate ◆given in the monograph◆.

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.]

With the apparatus operating at the rate specified ◆in the monograph,◆ add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for the minimum amount dissolved is met at an earlier time.◆

Method B—

Procedure ◆(unless otherwise directed in the individual monograph◆)—

ACID STAGE—Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage

unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified ◆in the monograph◆. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph◆.

BUFFER STAGE—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3 : 1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.]

Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.◆

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

IMMEDIATE-RELEASE DOSAGE FORMS

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 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 3*.

Dissolution Medium—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

DELAYED-RELEASE DOSAGE FORMS

Proceed as described for *Delayed-Release Dosage Forms, Method B* under *Apparatus 1 and Apparatus 2* using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Apparatus 4 (Flow-Through Cell)

IMMEDIATE-RELEASE DOSAGE FORMS

Place the glass beads into the cell specified ◆in the monograph◆. Place 1 dosage 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2,* using the specified media.

Time—Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

INTERPRETATION

Immediate-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 1*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient ◆specified in the individual monograph,◆ expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in *Acceptance Table 1* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q – 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

Acceptance Table 2

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.

Extended-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. 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.

Delayed-Release Dosage Forms

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA.

Acid Stage—Unless otherwise specified ◆in the individual monograph◆, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 3

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—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 4*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 4* is 75% dissolved unless otherwise specified ◆in the individual monograph◆. The quantity, Q,◆specified in the individual monograph◆ is the total amount of active ingredient dissolved in both the *Acid* and *Buffer Stages*, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in *Acceptance Table 4* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q – 15%.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

●2

(Official April 1, 2006)

BRIEFING

⟨**724**⟩ **Drug Release,** *USP 28* page 2415. It is proposed to revise this general test chapter where current text will become part of the harmonized text of *Dissolution* ⟨711⟩. The proposed change, which is being published in this *PF* for information only and is not for public comment, is scheduled for implementation in the *Second Interim Revision Announcement to USP 28–NF 23,* but with an delayed implementation date of **April 1, 2006**. Earlier implementation by individual companies may be done at their discretion.

(BPC: W. Brown) RTS—42047-1

Change to read:

⟨~~724~~⟩ ~~DRUG RELEASE~~

~~This test is provided to determine compliance with drug release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. [NOTE—Medium replacement is not necessary for *Ap-*~~

paratus 4, which is a continuous-flow system.] Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

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, 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.

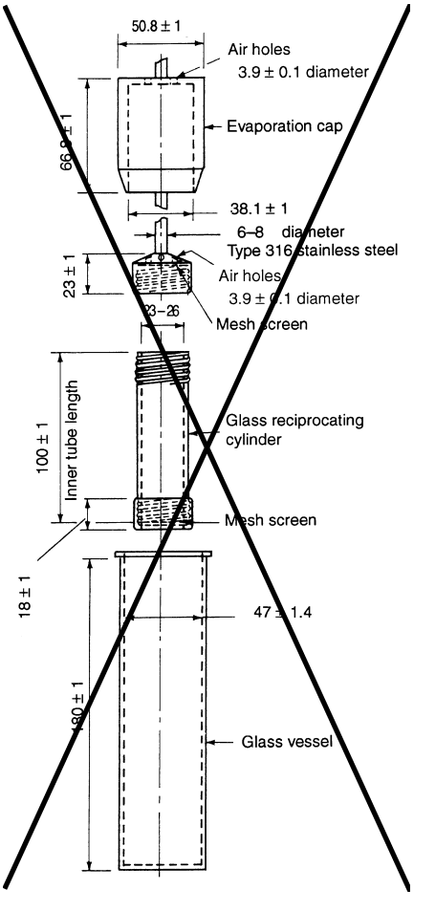


Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

USP Reference Standards ⟨11⟩ USP Chlorpheniramine Extended-Release Tablets RS *(Drug-Release Calibrator, Single Unit).*

Harmonization

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 Apparatus 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.

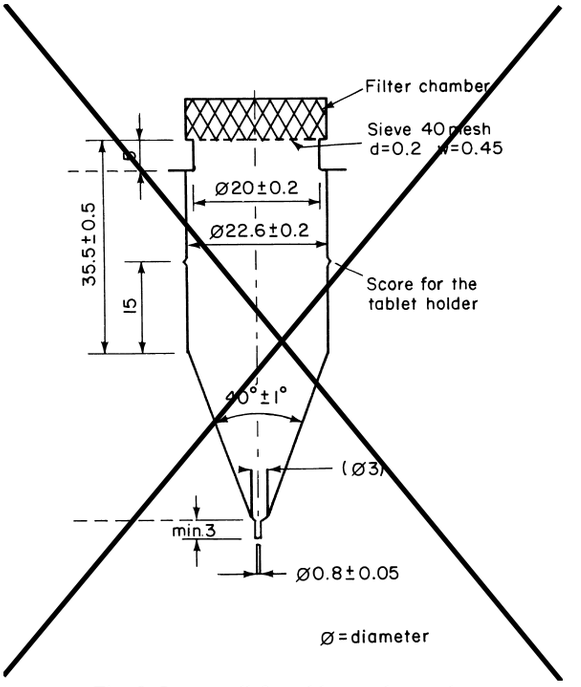


Fig. 2. Large cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

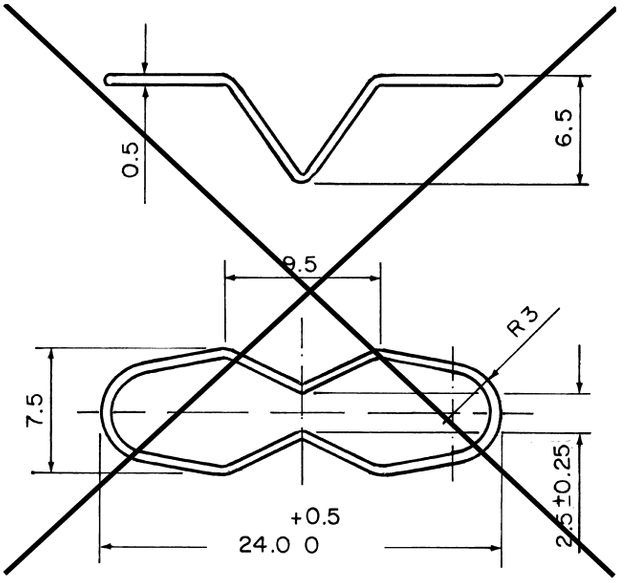


Fig. 2a. Tablet holder for the large cell.
(All measurements are expressed in mm unless noted otherwise.)

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°.

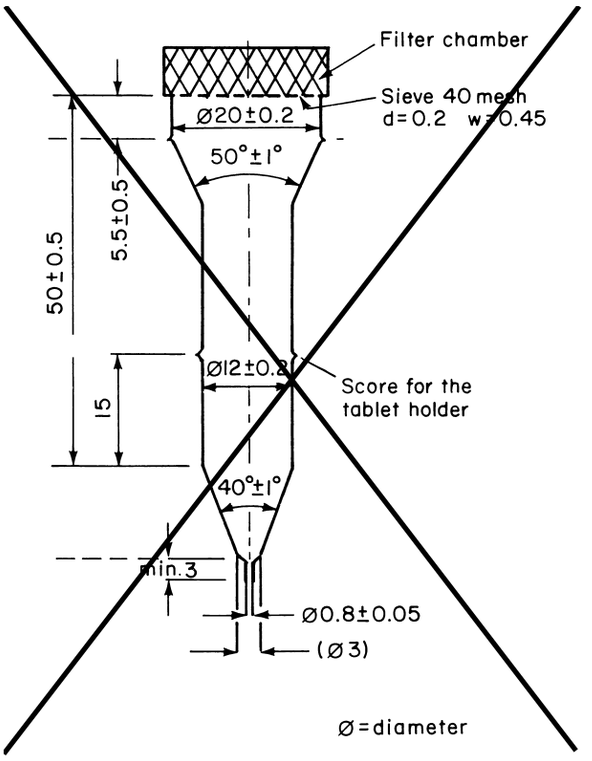


Fig. 3. Small cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

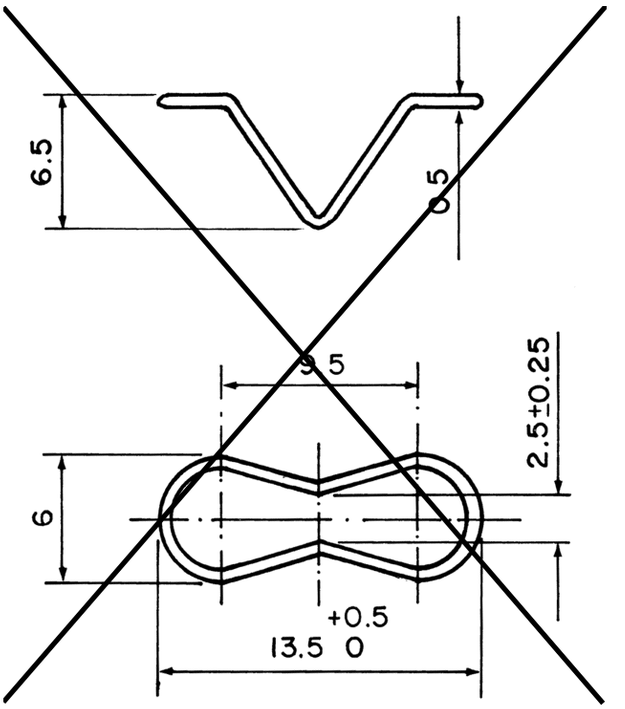


Fig. 3a. Tablet holder for the small cell.
(All measurements are expressed in mm unless noted otherwise.)

The 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⟩.

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 less 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 Apparatus 2*.

DELAYED-RELEASE (ENTERIC-COATED) ARTICLES—GENERAL DRUG RELEASE STANDARD

Use *Method A* or *Method B* and the apparatus specified in the individual monograph. Conduct the *Apparatus Suitability Test* as directed under *Dissolution* ⟨711⟩. All test times stated are to be observed within a tolerance of ± 2%, unless otherwise specified.

Method A

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph.

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed for *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 2

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier 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 3*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of *Q* in *Acceptance Table 3* is 75% dissolved unless otherwise specified in the individual monograph. The quantity, *Q*, specified in the individual monograph, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content. The 5% and 15% values in *Acceptance Table 3* are percentages of the labeled content so that these values and *Q* are in the same terms.

Acceptance Table 3

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q − 15%.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q − 15%, and no unit is less than Q − 25%.

Method B

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2* under *Method A*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Buffer Stage—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3 : 1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may be accomplished also by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.] Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Proceed as directed for *Interpretation* under *Method A*.

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

[1] Disk assembly (stainless support disk) may be obtained from Millipore Corp., Ashley Rd., Bedford, MA 01730.

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 [3]. 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*).

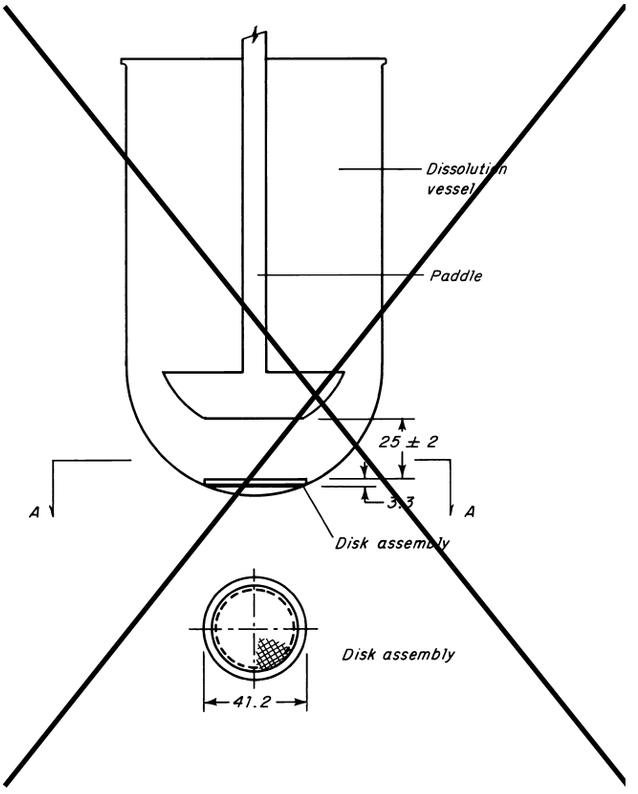


Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

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 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.

[3] A suitable device is the watchglass patch polytef mesh sandwich assembly available as the Transdermal SandwichTM from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

[3] Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, 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.

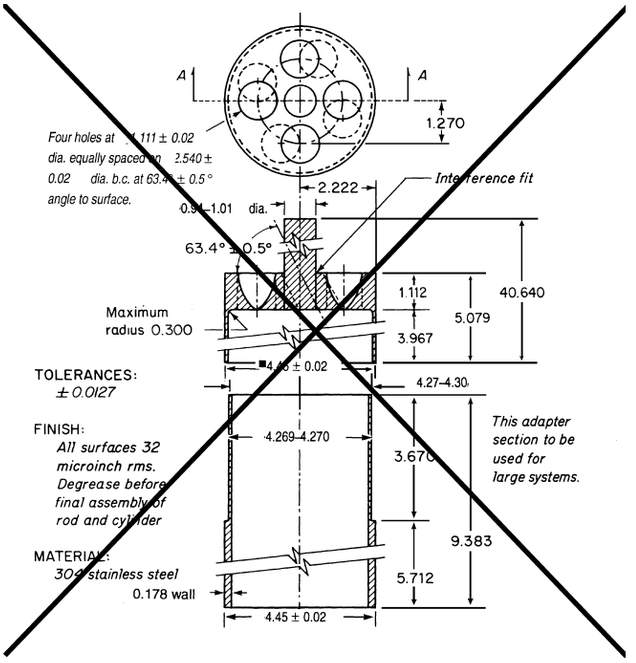


Fig. 5. Cylinder Stirring Element.[5]
(All measurements are expressed in cm unless noted otherwise.)

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 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.

Apparatus 7 (Reciprocating Holder)

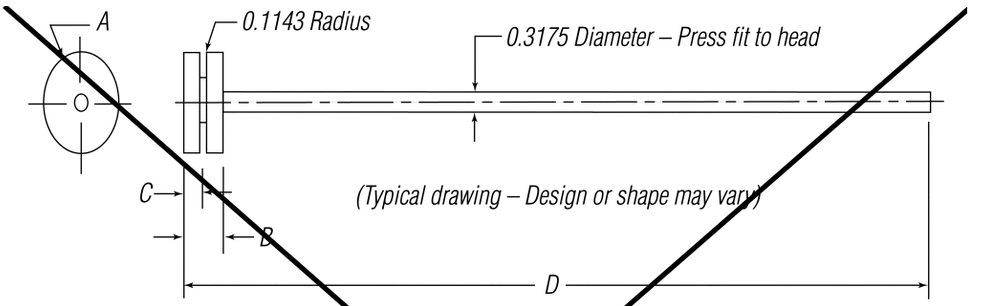
NOTE— This apparatus may also be specified for use with a variety of dosage forms.

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*[7] 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.

[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.

[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.

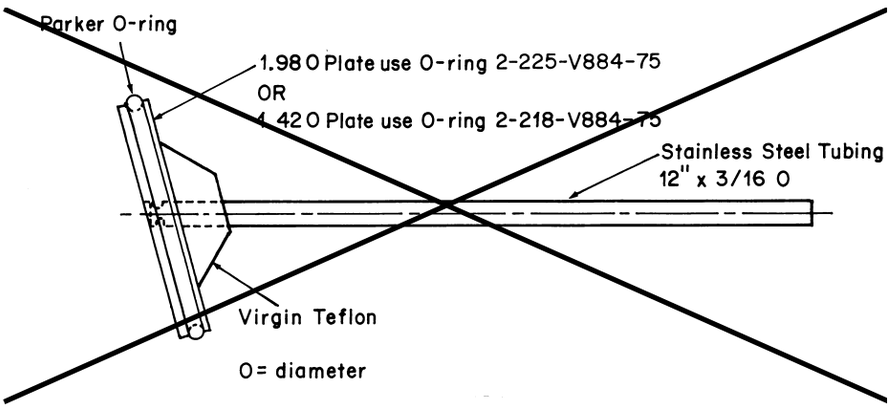


Dimensions are in centimeters

	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.[5]~~



~~Fig. 7a. Transdermal system holder—angled disk.~~

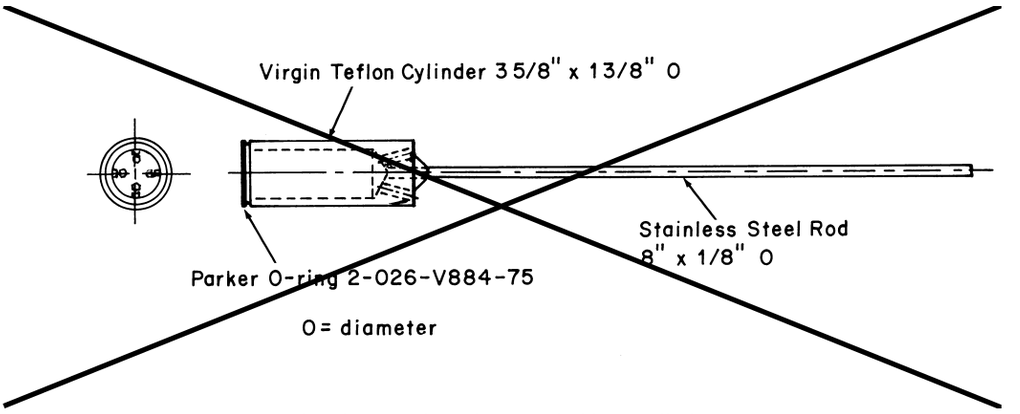


Fig. 7b. Transdermal system holder—cylinder.

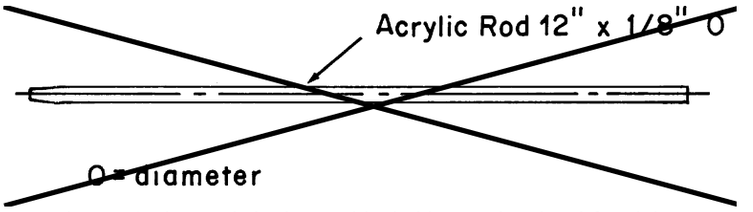
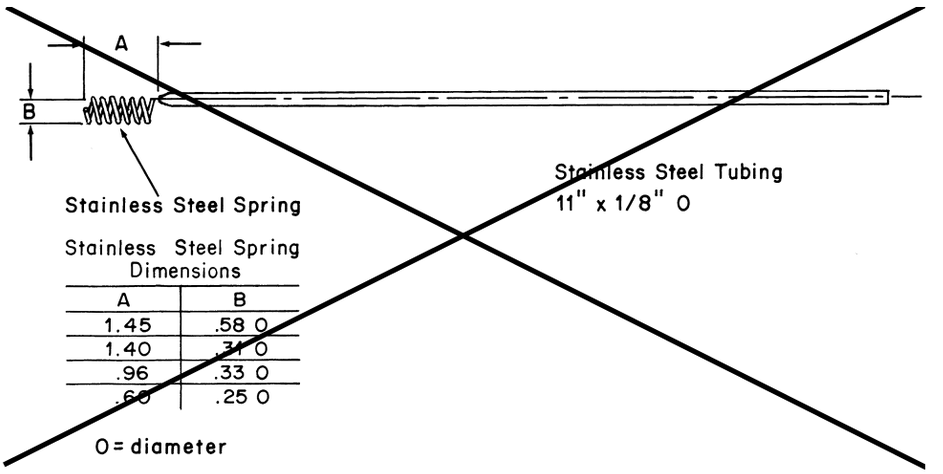


Fig. 7c. Oral extended-release tablet holder—rod, pointed for gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

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.~~

•⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at the temperature specified in the monograph or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

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 1*).

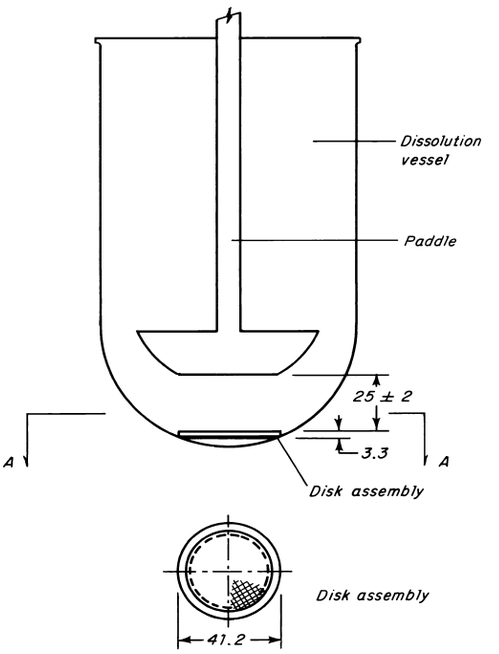


Fig. 1. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

[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 SandwichTM from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

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 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.

[3] Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, 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.

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 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 1

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 2*. 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.

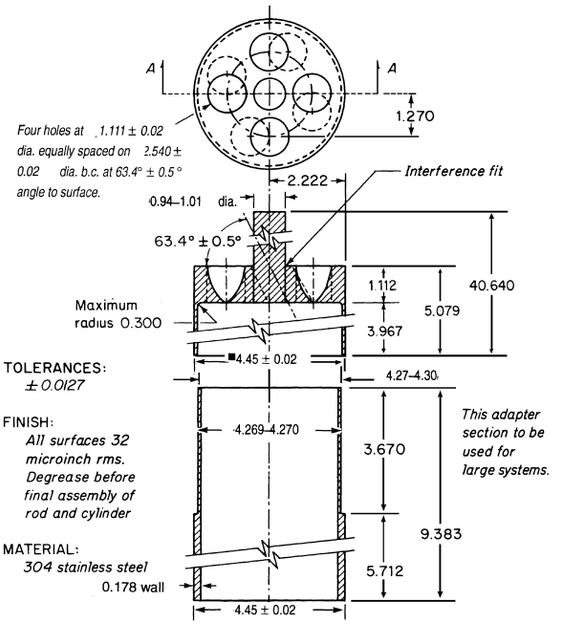


Fig. 2. Cylinder Stirring Element.[5]

(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 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*.

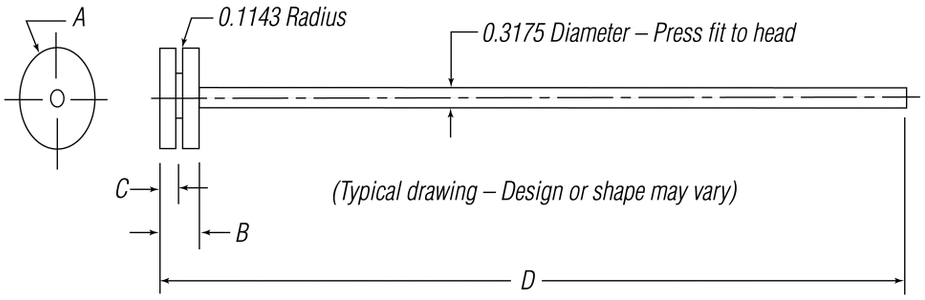
Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7 (Reciprocating Holder)

NOTE—This apparatus may also be specified for use with a variety of dosage forms.

[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.

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 3*[7] and Figures *4a–4d*). 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. 3. 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.

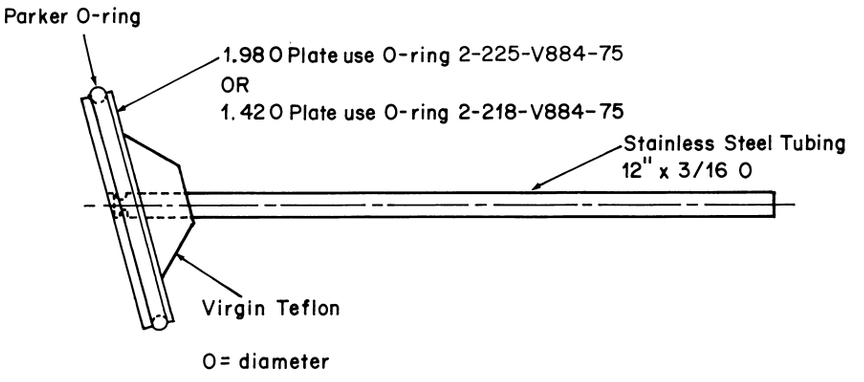


Fig. 4a. Transdermal system holder—angled disk.

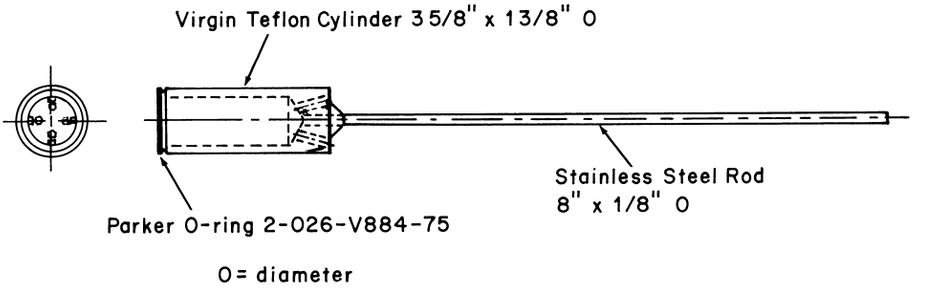


Fig. 4b. Transdermal system holder—cylinder.

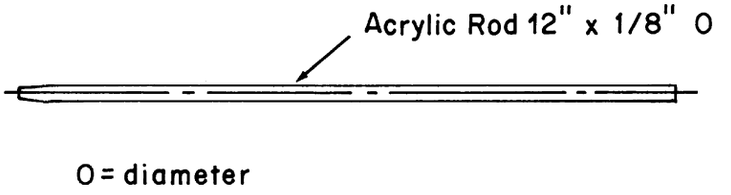
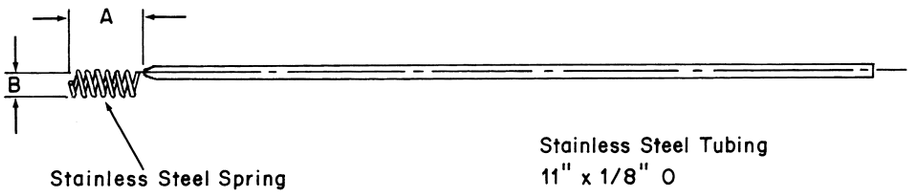


Fig. 4c. Oral extended-release tablet holder—rod, pointed for gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O = diameter

Fig. 4d. 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 2* under *Dissolution* ⟨711⟩ for coated tablet drug delivery systems, to *Acceptance Table 1* 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.●2

(Official April 1, 2006)

BRIEFING

⟨**811**⟩ **Powder Fineness,** *USP 28* page 2480. The United States Pharmacopeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopeia in the efforts toward the international harmonization of compendial standards for this general test chapter. The presented text represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **CONSENSUS STAGE 5B** draft. Because of significant changes, the draft has reverted to the **OFFICIAL INQUIRY STAGE 4**.

Proposed changes from the current USP General Chapter ⟨811⟩ *Powder Fineness* include the following:

(1) *In the opening paragraph (the introduction)*—References to USP General Chapters have been removed to further harmonization. Allowance for light diffraction methods is introduced.
(2) *Sieves for Pharmacopeial Testing*—This section that references USP General Chapters is omitted to further harmonization.
(3) *Powdered Vegetable and Animal Drugs*—This section is omitted based on comments that it is irrelevant for harmonization.
(4) *Air Permeation Method for Determining Fineness of Subsieve Size Particles*—This section is omitted based on comments that it would be better to describe this method separately. This paragraph is no longer referenced in a USP monograph.
(5) *Classification of Powder Fineness*—This section is completely revised to use ISO Standards. The term ''very coarse'' has been omitted from the draft based on comments that it is not used in *EP* or *JP*.

(ETM: J. Lane) RTS—41926-1

Add the following:

⟨811⟩ POWDER FINENESS

The particle size distribution should be estimated by analytical sieving or by application of other methods where practical. A simple descriptive classification of powder fineness is provided in this chapter. For practical reasons, sieves are commonly used to measure powder fineness. Sieving is most suitable where a majority of the particles are larger than about 75 μm, although it can be used for some powders having smaller particle sizes where the method can be validated. Light diffraction is also a widely used technique for measuring the size of a wide range of particles from very fine to coarse (0.1 μm to 8 mm).

Classification of Powder Fineness—Where the cumulative distribution has been determined by analytical sieving or by application of other methods, powder fineness may be classified in the following manner:

x_{90} = particle dimension corresponding to 90% of the cumulative undersize distribution;

x_{50} = median particle dimension (i.e., 50% of the particles are smaller and 50% of the particles are larger);

x_{10} = particle dimension corresponding to 10% of the cumulative undersize distribution.

It is recognized that the symbol d is also widely used to designate these values. Therefore, the symbols d_{90}, d_{50}, and d_{10} may be used.

The following parameters may be defined based on the cumulative distribution.

$Q_R(x)$ = cumulative distribution of particles with a dimension less than or equal to x where the subscript R reflects the type of quantity of the density distribution.

R	Distribution Type
0	Number
1	Length
2	Area
3	Volume

Harmonization

Therefore, by definition:

$Q_R(x) = 0.90$ when $x = x_{90}$

$Q_R(x) = 0.50$ when $x = x_{50}$

$Q_R(x) = 0.10$ when $x = x_{10}$

An alternative but less informative method of classifying powder fineness is by use of the terms in the following table.

Classification of Powders by Fineness

Descriptive Term	x_{50}	Cumulative Distribution by Volume Basis, $Q_3(x)$
Coarse	$x_{50} > 355$	$Q_3(355)$ 0.50
Moderately Fine	180 $x_{50} \leq 355$	$Q_3(180)$ 0.50 and $Q_3(355) \geq 0.50$
Fine	125 $x_{50} \leq 180$	$Q_3(125)$ 0.50 and $Q_3(180) \geq 0.50$
Very Fine	$x_{50} \leq 125$	$Q_3(125) \geq 0.50$

Harmonization

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.

GENERAL CHAPTERS

General Information

BRIEFING

⟨1058⟩ Analytical Instrument Qualification. This new general information chapter, which is being presented in *Pharmacopeial Previews,* reflects the conclusions of a 2003 workshop held in Arlington, Virginia, by the American Association of Pharmaceutical Scientists. Good Manufacturing Practices (GMP) regulations require companies to establish procedures ensuring the fitness for use of instruments that generate data supporting regulated product testing. However, GMP regulations do not provide definitive guidance for the qualification of analytical instruments. This chapter covers the initial part of the data quality acquisition process (qualification, validation, and verification), defines the roles and responsibilities of those associated with an instrument's qualification, and establishes the essential parameters for performing instrument qualification and a common terminology. It is recognized by the Expert Committee that the current chapter does not address corrective and preventive actions when a periodic performance qualification (PQ) check fails. Readers are encouraged to submit comments to USP regarding these or any other relevant issues.

(PA4: H. Pappa) RTS—41837-1

Add the following:

⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of instruments and tools, ranging from simple nitrogen evaporators to complex multiple-function technologies, are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use and that they do not pose high safety risks. Analysts' objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures and perform system suitability tests and in-process quality control checks to help ensure that the acquired data are reliable. These activities help enhance the quality of data, and there are specific guidance and procedures for performing the activities. With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions abound regarding instrument qualification and validation procedures and the roles and responsibilities of the people who perform them. Consequently, various approaches have been used for instrument qualification, which require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data.

Validation versus Qualification

Ambiguity exists in the use of the terms "validation" and "qualification". In this chapter the term "validation" is used for processes and software, and the term "qualification" is used for instruments. Therefore, the phrase "analytical instrument qualification" (AIQ) is used for the process of ensuring that an instrument is suitable for its intended application. The term "validation" is reserved for processes including analytical procedures and software procedures.

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the base for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control checks. These quality components are described below.

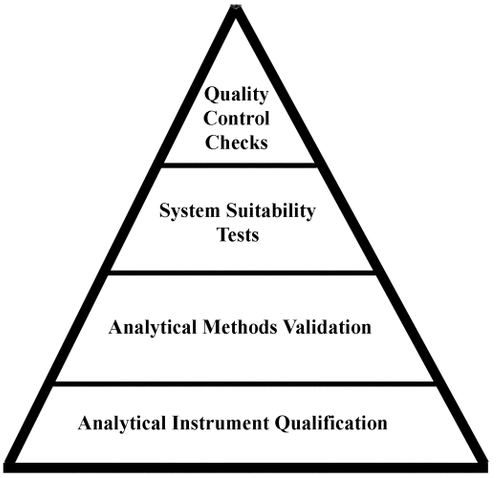


Fig. 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure does what it purports to do and addresses the required attributes of the procedure. Use of a validated procedure provides confidence that the procedure will generate test data of acceptable quality. Users of compendial procedures perform validation using the criteria provided in General Chapter *Validation of Compendial Methods* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform according to the analyst's expectations and the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure the system's acceptable performance at the time of the test. USP General Chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests.

Quality Control Checks

Most analyses are performed on instruments calibrated or standardized using reference materials or calibration standards. The calibration or standardization process uses a single- or multiple-point calibration, depending on the instrument and the intended application. The calibration or standardization of an instrument during analysis ensures that the instrument response correlates with the known quantity or quality of the calibration standard or reference material. In addition to calibration or standardization, some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance.

The extent of system suitability tests or quality control checks varies for different analyses, depending on their intended use. Chemical analyses, which are largely subject to Good Manufacturing Practices (GMP) regulations and require tighter precision and accuracy, may require more system suitability tests than bioanalytical work. This work—largely subject to Good Laboratory Practice (GLP) regulations and requiring sensitive, specific, broad-range analysis—is generally performed with more quality control checks during sample analysis. Control check samples are also appropriate when high-variability tests or instruments (i.e., those with a relative standard deviation [RSD] higher than 5%) are considered. Other use-specific considerations may also determine the extent of system suitability tests or quality-control-check sample analysis. Nevertheless, the sum total of such controls provides an important step in delivering quality data for the intended purpose.

In summary, analytical instrument qualification and analytical method validation ensure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks ensure the quality of analytical results *immediately before* or *during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical data—analytical method validation, system suitability tests, and quality control checks—are not within the scope of this chapter.

Qualification Phases

Instrument qualification is not a single continuous process but instead results from several discrete activities. For convenience, these activities can be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Some of these qualification terms have their roots in manufacturing-process validation. Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Also, some AIQ activities cover more than one qualification phase and could arguably be performed within any of the phases. It is important that the required AIQ activities be performed; it is not as important within which qualification phase an activity is performed or reported. *Table 1* accommodates these overlapping activities by letting users perform them under one or another phase as necessary. The user should describe where the activity is performed and reported.

Table 1: Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification*

DQ	IQ	OQ	PQ
	Timing and applicability		
Prior to purchase of a new type of instrument	At installation of each instrument (new, old, or existing unqualified)	After installation or major repair of each instrument	Periodically at specified intervals for each instrument
	Activities		
Assurance of vendor's DQ	System description ⇆	Fixed parameters	Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery		SOPs for operation, calibration, and maintenance
Instrument's fitness for use in laboratory	Utilities/facility/ environment		
	Network and data storage ⇆	Secure data storage, backup, and archive	
	Assembly and installation		
	Installation verification ⇆	Instrument functions tests ⇆	Performance checks

* Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Such activities spanning more than one qualification phase are shown as connected by double arrows. If an activity listed under a given phase is performed under another phase, it is not necessary to repeat the activity under the phase where the activity is listed. Performing the activity is far more important than the phase under which the activity is performed.

DESIGN QUALIFICATION

Design qualification (DQ) is most suitably performed by the instrument developer or manufacturer. Since the instrument design is already in place for commercial off-the-shelf (COTS) systems, users do not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature of the instrument, the complexity of the proposed application, and the extent of users' previous interaction with the manufacturer. Vendor audits or required vendor-supplied documentation satisfy

part of the DQ requirements. The required scope and comprehensiveness of the audits and documentation vary with users' familiarity with the instrument and their previous interactions with the vendor.

Informal processes also form an important part of DQ. Informal personal communications and networking with peers at technical or user-group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Another good source of information about suitability for intended use is informal site visits to other users' and vendors' facilities to obtain data on representative samples that used the specified instrument. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection.

INSTALLATION QUALIFICATION

Installation qualification (IQ) is the documented collection of activities necessary for installing an instrument in the user's environment. IQ applies to an instrument that is new or was preowned, or to any instrument that exists on site but has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been packed and transported to another location. The activities and documentation associated with IQ are as follows.

System Description—Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flow charts where appropriate.

Instrument Delivery—Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment—Verify that the installation site satisfactorily meets vendor specified environmental requirements. A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.

Network and Data Storage—Some analytical systems require users to provide network connections and data storage capabilities at the installation site. When required, connect the instrument to the network, and check its functionality.

Assembly and Installation—Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and install simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. If the preowned, unqualified existing instrument or transported instrument requires assembly and installation, perform the tasks as specified above, then perform the installation verification procedure, described below.

Installation Verification—Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and, when present, the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

OPERATIONAL QUALIFICATION

After a successful IQ, the instrument is ready for OQ testing. The OQ phase may consist of these test parameters.

Fixed Parameters—These tests measure the instrument's nonchanging parameters. like length, height, weight, voltage inputs, acceptable pressures, and loads. If the vendor-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need redetermination. [NOTE—These tests could also be performed during the IQ phase (see *Table 1*); if so, fixed parameters need not be redetermined as part of OQ testing.]

Secure Data Storage, Backup, and Archiving—When required, test secure data handling, such as storage, backup, and archiving, at the user's site according to written procedures.

Instrument Function Tests—Important instrument functions should be tested to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter. Nevertheless, as a guide to the type of tests possible during OQ, consider these, which apply to an HPLC unit:

- pump flow rate,
- gradient linearity,
- detector wavelength accuracy,
- detector linearity,
- column oven temperature,
- injector precision and accuracy, and
- peak retention time precision.

Routine analytical tests do not constitute OQ testing. OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment and may not be required to be repeated at regular intervals. Rather, when the instrument undergoes major repairs or modifications, relevant OQ tests should be repeated to verify whether the instrument continues to operate satisfactorily. Relevant OQ tests should also be repeated for an instrument that has been transported to another location, although a move within the laboratory, or from one room to another, that does not disturb instrument operation may not require requalification.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification and should be performed whenever possible. Holistic tests, which involve the entire system, are acceptable in lieu of modular testing. Having successfully completed OQ testing, the instrument is qualified for use in regulated samples analysis.

PERFORMANCE QUALIFICATION

After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through performance qualification (PQ). The PQ phase includes the following parameters.

Performance Checks—Set up a test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. PQ tests should be performed routinely on a working instrument, not only on a

new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble-free instrument operation for the intended applications. PQ tests should be performed independently of the routine analytical testing performed on the instrument. Like OQ testing, the tests can be modular or holistic. Because many modules within a system interact, holistic tests generally prove more effective because they evaluate the entire system, not simply the system's individual modules.

Testing frequency depends on the ruggedness of the instrument and the criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. Or it may be scheduled for regular intervals, such as weekly or monthly. Experience with the instrument can influence this decision. Generally, the same PQ tests are repeated each time so that a history of the instrument's performance can be compiled. Some system suitability tests or quality control checks that are performed concurrently with the test samples also imply that the instrument is performing suitably. However, although system suitability tests can supplement periodic PQ tests, they cannot replace them.

Preventive Maintenance and Repairs—When an instrument fails to meet PQ test specifications, it requires maintenance or repair. For many instruments a periodic preventive maintenance may also be recommended. The relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Standard Operating Procedure[s] for Operation, Calibration, and Maintenance—Establish standard operating procedures to maintain and calibrate the instrument. Use a logbook, binder, or electronic record to document each maintenance and calibration activity.

Roles and Responsibilities

USERS

Users are ultimately responsible for instrument operations and data quality. The users' group encompasses analysts, their supervisors, and organization management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments, because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, validation specialists, and quality assurance (QA) personnel can advise and assist as needed, but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

QUALITY ASSURANCE

The QA role in AIQ remains the same as for any other regulated study. QA personnel should understand the instrument qualification process, and they should learn the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it meets regulatory requirements and that the users attest to its scientific validity.

MANUFACTURERS

Manufacturers and developers are responsible for DQ when designing the instrument. They are also responsible for validation of relevant processes used in manufacturing and assembly of the hardware and for software associated with the instrument. Manufacturers and developers are also

responsible for writing stand-alone software for analytical work in a documented quality manner and for the validation of this software. Manufacturers should test the assembled instruments before shipping them to users.

Manufacturers and vendors should make available to users a summary of their validation efforts and the results of final instrument and software tests and should provide the critical functional test scripts that can be used to qualify the instrument and software at the user site. For instance, manufacturers and vendors can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, manufacturers and vendors should notify all known users about hardware or software defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

SOFTWARE VALIDATION

Software used for analytical work can be classified into three categories: firmware; instrument control, data acquisition, and processing software; and stand-alone software.

Firmware—Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users generally cannot alter firmware design or function. Firmware is thus considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware. So when the hardware (that is, the analytical instrument) is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see *Change Control,* below).

Instrument Control, Data Acquisition, and Processing Software—Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and postacquisition calculations. Thus both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire instrument and software system, is more efficient than modular validation of the software alone. Thus the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process.

Stand-Alone Software—An authoritative guide for validating stand-alone software, such as LIMS, is available.[1] The validation process is administered by the software developer, who also specifies the development model appropriate for the software. Validation takes place in a series of activities planned and executed through various stages of the development cycle.[1]

The software validation guide cited in the previous paragraphs indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only part of the validation process for stand-alone software and does not constitute

[1] *General Principles of Software Validation: Final Guidance for Industry and FDA Staff,* U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, January 11, 2002. http://www.fda.gov/cdrh/comp/guidance/938.html (accessed September 2004).

complete validation. Refer to the software validation guide for activities that must be performed at the user site for testing stand-alone software used in analytical work.

Change Control

Changes to the instrument and software become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required. The change control process enables them to do this.

Change control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below:

Operational Qualification—Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.

Performance Qualification—Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In future, perform the revised PQ testing.

For changes to firmware and to software for instrument control, data acquisition, and processing, change control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change control for stand-alone software requires user-site testing of changed functionality.

AIQ Documentation

Two types of documents result from AIQ: static and dynamic.

STATIC DOCUMENTS

Static documents are obtained during the DQ, IQ, and OQ phases and should be kept in a ''Qualification'' binder. Where multiple instruments of one kind exist, documents common to all instruments should go into one binder or section, and documents specific to an instrument should go into that instrument's binder or section. During change control, additional documents can be placed with the static ones, but previous documents should not be removed. When necessary, such documents may be archived.

DYNAMIC DOCUMENTS

Dynamic documents are generated during the OQ and PQ phase when the instrument is maintained or tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them. These documents may also be archived as necessary.

Instrument Categories

Modern laboratories typically include a suite of tools varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of prin-

ciples to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Each group is illustrated by some example instruments. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site, which should be determined by users for their specific instruments or applications.

GROUP A

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Example instruments in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, and glass pipets.

GROUP B

Conformance of Group B instruments to user requirements is performed according to the instruments' standard operating procedures. Their conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple, and causes of their failure are readily discernible by simple observations. Example instruments in this group are balances, incubators, infrared spectrometers, melting point apparatus, muffle furnaces, light microscopes, pH meters, variable pipets, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, and viscosimeters.

GROUP C

Conformance of Group C instruments to user requirements is complex and highly method specific, and conformity bounds are determined by the application. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Example instruments in this group include the following:

- atomic absorption spectrometers,
- differential scanning calorimeters,
- electron microscope,
- flame absorption spectrometers,
- high-pressure liquid chromatographs,
- mass spectrometers,
- microplate readers,
- thermal gravimetric analyzers,
- X-ray fluorescence spectrometers,
- densitometers,
- diode-array detectors,
- elemental analyzers,
- gas chromatographs,
- near IR spectrometers,
- Raman spectrometers,
- UV/Vis spectrometers, and
- inductively coupled argon–plasma emission spectrometers.

Again, it must be emphasized that the placement of these instruments in the given three groups are for illustrative purposes only. The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

CONCLUSION

The purpose of the use of analytical instruments is to generate reliable data. Analytical instrument qualification helps fulfill this purpose. No authoritative guide existed that considered the risk of instrument nonperformance and combined that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments became a subjective and often fruitless document-generating exercise.

This chapter is based on the outcome of a user workshop-conference on the subject and provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The process provided in this chapter focuses on scientific value rather than on producing documents. Implementing such a process should increase efficiency and remove ambiguous or varying interpretations by various groups.

BRIEFING

⟨1090⟩ In Vivo Bioequivalence Guidances. A new version of this USP general information chapter, entitled *Drug Product Interchangeability,* is being previewed in this issue of *PF.* The new version of this chapter presents the different approaches used by regulatory authorities to assess drug product interchangeability in order to establish national markets for reference products and generic equivalents. The text discusses the relationships among WHO, ICH, FDA, and USP approaches from the following perspectives: specifications; bioavailability (BA), bioequivalence (BE), and dissolution; WHO and FDA interchangeability approaches; and methodology for BE studies and waivers for in vivo studies. Interested parties are encouraged to submit comments.

(BPC: H. Pappa) RTS—41913-1

Change to read:

⟨1090⟩ ~~IN VIVO BIOEQUIVALENCE GUIDANCES~~ DRUG PRODUCT INTERCHANGEABILITY

In many countries, drug products (medicines) enter the marketplace only after evaluation of safety, efficacy, and quality information by a national drug regulatory authority. Many of the requirements and recommendations for the kind of data to be submitted to these authorities by an applicant are specified in national laws, regulations, and guidances. Through the World Health Organization (WHO) and the International Conference on Harmonization (ICH), the type of information needed to support a regulatory filing has been clarified and, where feasible, harmonized. Adoption of a WHO document by a regulatory authority is optional. For countries participating in ICH, adoption is required after agreement is reached on the harmonized document. The ICH documents then become allied with additional national or regional requirements and recommendations as a means of informing applicants about optimal ways to develop information in a regulatory filing. WHO, but not ICH, has developed guidances that consider bioavailability (BA), bioequivalence (BE), and dissolution studies and their role in assuring product performance in an initial regulatory filing and following approval. Well-evolved national systems that promote a system of interchangeable multisource drug products have arisen in the U.S. and elsewhere. In these settings, a national drug regulatory authority determines whether a dosage form is pharmaceutically equivalent and bioequivalent to a defined reference product. If this determination is positive, the dosage form is declared to be therapeutically equivalent and hence interchangeable with

the reference product. These systems rely on various types of studies to document pharmaceutical equivalence and bioequivalence. For bioequivalence, both in vivo clinical studies (e.g., pharmacokinetic, pharmacodynamic, and clinical) are used as well as in vitro dissolution studies. In addition, dissolution techniques are also used for nonsolution orally administered and other drug products to control quality. Given that they apply to both the reference product and interchangeable multisource drug products, public drug substance and drug product monographs in the *USP–NF* help assure interchangeability of drug substances and drug products.

The relationships among WHO, ICH, FDA, and USP approaches are similar and at times identical. The purpose of this general information chapter is to discuss these relationships from the following perspectives: (1) specifications; (2) BA, BE, and dissolution; (3) WHO and FDA interchangeability approaches; and (4) methodology for BE studies.

SPECIFICATIONS

Information in a regulatory filing about the safety, efficacy, and quality of a drug product is closely related. Safety and efficacy are established in clinical and nonclinical trials using active and inactive ingredients and products that are subjected to extensive physicochemical and other characterization tests. As part of the regulatory approval process, a subset of these tests is used in a private set of specifications, at times allied with public standards in *USP–NF* that control the quality of the drug product to its expiry date. In the ICH document *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (Q6A), a specification is defined as a series of tests, procedures, and acceptance criteria for an ingredient, a product, its packaging material, or other components used in the manufacturing process. Many of these private specifications subsequently become public via Pharmacopeial processes and are presented, together with other requirements, in ingredient and product monographs in *USP–NF* and other pharmacopeias. Specifications are adequate to control quality only when important manufacturing factors (method of manufacture, components, and composition) are invariant relative to the manufacturing factors that created the clinical trial material on which safety and efficacy data were generated. With changes in method of manufacture of the drug product and/or its ingredients, additional recharacterization information may be needed to assure the continuing quality and performance of the drug product. This information can be submitted in postapproval regulatory filings that undergo scrutiny in a manner similar to that for an original application. Maintenance of key quality attributes reflected in these approaches work to assure practitioners and patients that the requisite safety and efficacy outcomes will be achieved with administration of the drug product.

Standards in a Pharmacopeial monograph include introductory statements (definition, description, packaging and storage statements), followed by the public specification for the ingredient or product (article). When an article is shown by testing and other scrutiny to conform to the stipulations of its monograph, the identity of the article is established. The specifications in *USP–NF* ingredient and product monographs allow the public at large to understand better how the quality of a drug product is controlled. Furthermore, monograph standards help assure interchangeability across ingredients and products with the same name, which should be tested using the same procedures and acceptance criteria when appropriate. Private specifications help control the quality of a specific set of ingredients that are combined in a specific product. Public specifications help control the quality of all ingredients and

products bearing the same name. Thus while a public and private specifi-cation may be closely related, differences exist to account for different routes of synthesis and manufacturing processes. Increasingly, these differences will be accounted for in *USP–NF* monographs. Taken together, the work of a regulatory authority and USP are closely allied, with each performing different yet complementary functions. For example, the regulatory authority generally establishes acceptance criteria for impurities, given that these are closely related to safety and efficacy information. *USP–NF* provides generally useful validated analytical procedures with acceptance criteria that are applicable to many ingredients and products.

BIOAVAILABILITY, BIOEQUIVALENCE, AND DISSOLUTION

Except for solution dosage forms, where bioavailability is usually considered self-evident, bioavailability (BA) and bioequivalence (BE) information is considered important in a regulatory filing. Although BA information may be part of a data set that broadly addresses the absorption, distribution, metabolism, and excretion (ADME) of the active ingredient, product quality BA and BE studies focus on the performance of the drug product. For an innovator product, BA requires no comparator product in that it establishes the performance of the to-be-marketed drug product or precursor clinical trial material, even though this performance may be evaluated relative to a solution, suspension, parenteral, or other type of dosage form as reference. BE data are necessarily comparative in that a BE study assesses the performance of two drug products—the test (T) and reference (R) product. Although not specifically mentioned, BA and BE studies conform to the general approaches delineated in the ICH Q6A document, i.e., they are characterization studies that establish, for purposes of a regulatory filing, the performance of a specific drug product. In this context, disintegration or dissolution tests with acceptance criteria, which are specifically mentioned in ICH Q6A, may become one of a series of tests in the drug product specification. The BE characterization test is more determinative than the in vitro dissolution or disintegration batch release test, i.e., bioequivalent drug products may still rely on different dissolution or disintegration procedures and acceptance criteria to assess performance. Over time, the private dissolution or disintegration test may become the public performance test in *USP–NF*. Both the private and public approaches frequently rely on suitably validated and calibrated disintegration, dissolution, and other procedures provided in *USP–NF* general chapters. Determinations about BA and BE are regulatory in character. The USP performance test is related to BA and BE only when closely allied with a sound regulatory determination. Without this link, the USP performance test should be regarded solely as a quality control test for batch release.

INTERCHANGEABILITY

The challenge of moving towards a fully evolved system of innovator (R) and interchangeable (generic) drug products (T) exists in many countries and regions of the world. In the U.S., reference products, termed the reference listed drug, are so noted in FDA's *Approved Drug Products with Therapeutic Equivalence Ratings* (Orange Book), which is

updated monthly (http://www.fda.gov/cder/ob). Although the pioneer product is usually the reference product (R), this is not always the case. To assist countries and regions where the reference product may not always be readily identifiable, the WHO has prepared a document entitled *Guidance on the Selection of Comparator Pharmaceutical Products for Equivalence Assessment of Interchangeable Multisource (Generic) Products.* With a clearly defined set of reference products, the task for a country or region becomes one of requiring that a manufacturer demonstrate, to the satisfaction of its regulatory authority, that its multisource product is pharmaceutically equivalent and bioequivalent to the corresponding reference product.

Many documents are available throughout the world to help applicants understand BA and BE requirements and recommendations. These approaches have become increasingly important as countries and regions move to legal systems that support the availability of innovator and interchangeable multi-source products. These systems necessarily rely on some definition of pharmaceutical equivalence and a further requirement that two drug products (T and R) must be both pharmaceutically equivalent and bioequivalent in order to be therapeutically equivalent and thus interchangeable under all conditions of use. WHO and FDA documents provide extensive recommendations on the topic. There is substantial correspondence between the WHO and FDA approaches, which reflects the harmonization that has already occurred. Sometimes differences in terminology and other approaches exists. A comparison between WHO and FDA approaches is provided in *Table 1.*

Table 1—FDA and WHO Definitions

	FDA	WHO
Pharmaceutical Equivalents	Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, use the same route of administration, and are identical in strength or concentration. Pharmaceutically equivalent drug products are formulated to meet the same or compendial or other applicable standards, but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients, expiration time, and, within certain limits, labeling.	Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. However pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.
Pharmaceutical Alternatives	Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths.	

Table 1—FDA and WHO Definitions *(Continued)*

	FDA	WHO
Therapeutic Equivalents	Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[1]	Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and after administration in the same molar dose their effects, with respect to both efficacy and safety, will be essentially the same, all determined from appropriate studies (bioequivalence, pharmacodynamic, clinical or in vitro studies).
Bioavailability	The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.	The rate and extent of availability of an active drug ingredient from a dosage form as determined by its concentration-time curve in the systemic circulation or by its excretion in urine.
Bioequivalent Drug Products	This term describes pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions.[2]	Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.
Reference Products	A reference listed drug (21 CFR 314.94[a][3]) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.	A reference product is a pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety, and quality have been established and documented.

Table 1—FDA and WHO Definitions *(Continued)*

	FDA	WHO
Generic Products		A generic product is a pharmaceutical product, usually intended to be interchangeable with the innovator product. It is usually manufactured without a license from the innovator company and marketed after the expiry of patent or other exclusivity rights.
Multisource Pharmaceutical Products		Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.
Interchangeable Pharmaceutical Products		An interchangeable pharmaceutical product is one that is therapeutically equivalent to a reference product.

[1] FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with current Good Manufacturing Practices regulations.

[2] Section 505(j)(7)(B) of the Act describes one set of conditions under which a test and reference listed drug shall be considered bioequivalent: the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate. Bioequivalence may sometimes be demonstrated using an in vitro bioequivalence standard, especially when such an in vitro test has been correlated with human in vivo bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

World Health Organization

In 1995, WHO developed a guidance entitled *Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability (WHO Guideline).* This document provides recommendations to manufacturers and drug regulatory authorities on the information required to support a regulatory decision regarding the interchangeability between a multisource product (T) and a corresponding innovator (R) product. The WHO Guideline is part of a series of normative documents available to countries throughout the world on approaches to assure the quality of medicines. The guideline is abstracted in this section and is available at www.who.int.

Introduction—The *Introduction* acknowledges that conformity to current Good Manufacturing Practices (cGMPs) and pharmacopeial standards may be sufficient to assure interchangeability for many solution dosage forms. The *Introduction* also speaks to the scope of the guideline, which excludes complex active ingredients, and notes that it is provided without prejudice to intellectual property considerations.

Glossary—The *Glossary* to the WHO Guideline defines several important terms (bioavailability, bioequivalence, dosage form, therapeutic equivalence, generic product, innovator pharmaceutical product, interchangeable pharmaceutical product, multisource pharmaceutical product, pharmaceutical equivalence, reference product). These definitions provide the regulatory and science/technical basis for determining interchangeability. Definitions of the terms *pharmaceutical equivalence* and *bioequivalence* are particularly important. Pharmaceutical equivalence is established if two drug products contain the same amount of the same active substance(s), if they meet the same or comparable standards, and if they are intended to be administered by the same route. Although pharmaceutical equivalence has elements that are satisfied by definition (same route of administration and same dosage form), a determination that the active ingredient in a T product is the same as that in an R product might require extensive characterization studies depending on the complexity of the molecule. The allowance for dosage forms with different names is an important aspect of pharmaceutical equivalence and requires both regulatory and compendial judgment. In the U.S., for example, capsules and tablets are not considered pharmaceutically equivalent, although they might be considered pharmaceutically equivalent in other market zones. The WHO Guideline notes the importance of considering BA and BE not only in terms of rate and extent of absorption but also in terms of systemic exposure patterns. Noting various interpretations of the term *generic product*, the document expresses a preference for the term *interchangeable pharmaceutical product.* The WHO Guideline corresponds to U.S. approaches delineated at 21 Code of Federal Regulations (CFR) 320.

Part One: Regulatory Assessment of Interchangeable Multisource Pharmaceutical Products—The WHO Guideline emphasizes the importance of authorization by a regulatory authority as a means of allowing market access. Alternatively, where regulatory resources are limited, reliance on the WHO certification scheme may be useful. The latter approach, however, may not satisfy a national interest in assuring interchangeability. A WHO certificate does not usually indicate a determination of interchangeability. Secondly, even if such a determination were made, it would apply to the innovator product in the exporting country, a product that might not have the same quality and performance characteristics as that of the innovator product in the importing country.

The WHO Guideline notes that differences between multisource and innovator products may be obvious and unimportant (e.g., differences in appearance), while others may be less obvious but more important (e.g., excipients, stability, instructions for use, packaging). The section emphasizes the importance not only of a conclusion of therapeutic equivalence but also the need for manufacture according to GMPs, labeling, and other considerations. For orally administered dosage forms, excipients in a multisource product and in a corresponding innovator product do not have to be the same, although practitioners and patients should be aware that patients may respond differently to some excipients. The remainder of the section focuses on (1) technical data for regulatory assessment; (2) product information and promotion; (3) collaboration between drug regulatory authorities; and (4) exchange of evaluation reports as a means of conserving regulatory resources. A compendial monograph for the ingredients in a drug product and for the drug product itself can satisfy several elements in the list of required technical data.

Part Two: Equivalence Studies Needed for Marketing Authorization—The WHO Guideline lists the studies needed to document equivalence, allowing comparative bioequivalence studies, comparative pharmacodynamic studies, clinical studies, and in vitro dissolution. For most nonsolution dosage forms, bioequivalence may be satisfied either with bioequivalence studies or with in vitro dissolution studies. The WHO Guideline uses the term bioequivalence to indicate a pharmacokinetic study. In the U.S., the term bioequivalence is used to indicate any study—pharmacokinetic, pharmacodynamic, clinical, or in vitro dissolution study—used to document comparable product performance.

The WHO Guidance recommends in vivo studies for the following dosage forms:

- bioproblem drugs
- transdermal patches, suppositories
- modified-release products
- fixed combinations of two or more active ingredients
- locally acting, nonsolution pharmaceutical products

In vitro studies may be adequate for all other dosage forms and for lower strengths of some of the dosage forms for which in vivo studies are recommended. The general approaches in this section of the WHO Guidance correspond to U.S. approaches for products approved prior to 1962. After that date, FDA generally required an in vivo bioequivalence study, although more recently FDA has allowed increased reliance on in vitro dissolution studies within the recommendations of the biopharmaceutics classification system (BCS).

Part Three: Tests for Bioequivalence—The WHO Guideline provides detailed recommendations regarding the conduct of pharmacokinetic studies in humans and brief descriptions of pharmacodynamic and clinical studies. The WHO Guidance notes that where in vitro dissolution is used to document equivalence, an in vivo-in vitro correlation (IVIVC) may be required or, alternatively, a multi-source and an innovator product may be considered equivalent if both are rapidly dissolving (80% in 15 minutes). The latter approach is partial implementation of the Biopharmaceutical Classification System (BCS) (see below), while the former may be unnecessary, given that the requirements to document an IVIVC may be more burdensome than just showing BE via a single in vivo study. For all comparisons, the WHO Guidance recommends the use of an average criterion to assure interchangeability.

Concluding Parts—The closing sections of the WHO Guideline provide additional information on the following: in vitro dissolution tests in product development and quality control (Part 4); clinically important variations in bioavailability leading to nonapproval of the product (Part 5); studies needed to support new post-marketing manufacturing conditions (Part 6); and choice of reference product (Part 7). Part 7 was considered in more detail in the previously mentioned WHO *Comparator Pharmaceutical Product Guidance.*

Food and Drug Administration

In the past, FDA provided drug-specific guidances to sponsors who wished to perform bioequivalence studies. With minor modifications, these were published in *In Vivo Bioequivalence Guidances* ⟨1090⟩. More recently, FDA has issued or plans to issue general guidances on the topic, with the goal of reducing drug-specific guidances (http://www.fda.gov/cder/guidance/index.htm). A list of these guidances, together with their status, appears below:

- *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations (General Guidance)*
- *Statistical Approaches to Establishing Bioequivalence*
- *Bioanalytical Method Validation*
- *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*
- *Food-Effect Bioavailability and Fed Bioequivalence Studies*
- *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (draft);*
- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*
- *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*

Given that BA/BE studies are especially relevant for orally administered solid and nonsolution liquid oral dosage forms, the central guidance in this set of guidances is the *General Guidance.* This guidance is composed of six primary sections that are abstracted in the following paragraphs.

Section I—The *Introduction* states that the General Guidance addresses how to meet the BA and BE requirements set forth in 21 CFR part 320 as they apply to orally administered drug product and to other drug products where reliance on systemic exposure measures is suitable to document BA and BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). The Guidance supports (1) BA and BE studies conducted during the Investigational New Drug (IND) period for a New Drug Application (NDA), (2) BE studies intended for submission in an Abbreviated New Drug Application (ANDA), and (3) BE studies conducted in the postapproval period for certain changes in both NDAs and ANDAs. These statements emphasize the need to document links between the clinical trial material used to document safety and efficacy, where BA is established, and, via BE studies, between subsequent iterations of both pioneer and generic dosage forms.

Section II—*Background* provides the legal basis for the requirement of BA and BE studies, which is expressed in terms of the rate and extent of absorption. While rate of absorption is difficult to measure, the legal requirement is satisfied by systemic exposure measures, e.g., concentration-time curves of either parent drug or a relevant metabolite. The *Background* notes that BA may be part of a more

comprehensive set incorporating ADME data. Establishing product quality BA is a benchmarking effort for an innovator product. In contrast, documenting BE is usually a more formal comparative test that uses specified criteria for comparisons and predetermined BE acceptance criteria.

Section III—*Methods to Document BA and BE* indicates that (1) pharmacokinetic, (2) pharmacodynamic, (3) clinical, and (4) in vitro dissolution studies may be used to document BA and establish BE. The section notes the value of replicate study designs and provides a representative pharmacokinetic study design. The section also endorses the value, in BA and BE studies, of including in the study population individuals representative of the general population. After consideration of pharmacodynamic and clinical studies, the section concludes with the discussion of dissolution both as a means of measuring BA and BE and as a quality control test, i.e., one test in a series of tests forming the drug product specification.

Section IV—*Comparison of BA Measures in BE Studies* recommends an equivalence approach. This approach relies on (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) a BE limit (acceptance criteria or ''goalpost''). Log-transformation of exposure measures prior to statistical analysis should be performed. Although the General Guidance recommends an average criterion, it allows the possibility of other criteria that better assess a determination of interchangeability (see the FDA Guidance *Statistical Approaches to Establishing Bioequivalence*). The FDA Guidance recommends goalposts of 80%–125% for all products irrespective of whether the active ingredient in a T and R product is or is not defined as having a narrow therapeutic range (see also *Section VI*).

Section V—*Documentation of BA and BE* recommends an in vivo BE study for all solid oral dosage forms approved after 1962 and for bioproblem drug products approved prior to 1962. The section also establishes when a waiver of in vivo studies for different strengths of a drug product may be granted. The section then comments on specific recommendations for BA and BE studies depending on type of dosage form (solutions, suspensions, immediate-release products [capsules and tablets], modified-release products [delayed-release products and extended-release], and miscellaneous dosage forms).

Section VI—*Special Topics* provides comments and recommendations on (1) food-effect studies, (2) moieties to be measured, (3) long half-life drugs, (3) first point C_{max}, (4) orally administered drugs intended for local action, and (5) narrow therapeutic range drugs.

FDA has provided two guidances that address the use of dissolution both for regulatory and quality control purposes. The first of these is entitled *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* and the second is entitled *Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations*. USP general information chapter ⟨1088⟩ also provides useful information on the development of an IVIVC correlation.

METHODOLOGY FOR BIOEQUIVALENCE STUDIES

BE can be evaluated by comparing the in vivo rate and extent of drug absorption of a test and reference formulation in healthy subjects. In a standard in vivo bioequivalence study design, study participants receive test and reference products on separate occasions, in either single or multiple doses, with random assignment to the two possible sequences of product administration. Samples of an accessible biologic fluid such as blood or urine are analyzed for drug and metabolite concentrations, and pharmacokinetic parameters (AUC, C_{max} and T_{max}) are obtained from the resulting con-

centration-time curves. These pharmacokinetic parameters are then analyzed statistically to determine if the test and reference products yield comparable values.

Single-Dose Fasting Two-Way Crossover Design

Objective—The objective is to compare the rate and extent of absorption of a generic product with that of the reference-listed product when administered in equal labeled doses.

Design—The study design is a single-dose, two-treatment, two-period, two-sequence crossover with an adequate washout period (usually equal to at least 10 elimination half-lives of the drug) between the two phases of the study. An equal number of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocol should be approved by an institutional review board.

Facilities—Clinical facilities and analytical laboratory used for the study should be identified along with the names, titles, and curriculum vitae of the medical and scientific or analytical directors.

Selection of Subjects—The sponsor should enroll a number of subjects sufficient to ensure statistical validity of the study. It is recommended that a minimum of 24 subjects be used in this study. More subjects may be required for a drug that exhibits high intra-subject variability in metrics of rate and extent of absorption. Subjects should be healthy, preferably nonsmoking, volunteers 18 to 50 years of age, and within 10% of ideal body weight for height and build, although within 15% of ideal body weight is acceptable (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be accepted on the basis of acceptable medical history, physical examination, and clinical laboratory tests. Female subjects must be given a pregnancy test prior to beginning the study. Subjects with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. If smokers are included, they should be identified as such. Written, informed consent must be obtained from all subjects before they are accepted into the study.

Procedure—Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 mL of water. They should continue fasting for 4 hours after administration of the test or reference treatment.

Restrictions—Study volunteers should observe the following restrictions:

a. No alcohol- or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.
b. Subjects should take no Rx medications, including oral contraceptives, beginning two weeks prior to and no OTC medications beginning one week prior to initiation of the study and until after the study is completed.
c. Water may be taken except for 1 hour before and after administration, when no liquid is allowed other than that needed for drug dosing.
d. All meals during the study should be standardized, and the same meals should be served during both phases of the study.

Blood Sampling—In addition to the predose (0 hour) sample, venous blood samples should be collected postdose so that there are at least four sampling time points on the ascending part and six or more on the descending part of the concentration-time curve. The biological matrix (plasma, serum, or whole blood) should be immediately frozen after collection and, as appropriate, centrifuged, and kept frozen until assayed.

Subject Monitoring—Blood pressure and pulse rate should be monitored hourly during the first 4 hours of the study. Subjects with a heart rate <45 or >110 beats per minute should have an electrocardiogram (lead II) performed and have their pulse monitored hourly. Subjects should report any unusual symptoms observed during the study. Subjects should be periodically questioned during each phase of the study for any unusual symptoms experienced after drug administration.

Analysis of Blood Samples—The active ingredient should be assayed using a suitable analytical method validated with regard to specificity, accuracy, precision (both within and between days), limit of quantitation, linearity, and recovery. Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. If the analytical method is a chromatographic method, chromatograms of unknown samples, including all associated standard curve and quality control chromatograms, should be available for regulatory authorities.

Pharmacokinetic Analysis of Data—Calculation of area under the plasma concentration-time curve to the last quantifiable concentration (AUC_{0-T}) and to infinity ($AUC_{0-\infty}$), C_{max}, T_{max}, and $T_{1/2}$ should be performed according to standard techniques.

Statistical Analysis of Pharmacokinetic Data—The log transformed AUC and C_{max} data should be analyzed statistically using ANOVA. These two parameters for the test product should be shown to be within 80% to 125% of the reference product using the 90% confidence interval criterion.

Clinical Report, Side Effects, and Adverse Reactions—Subject medical histories, physical examination and laboratory reports, and all incidents of possible adverse reactions to the study formulations should be reported.

Multiple-Dose Steady State, Two-Way Crossover Design under Fasting Conditions

Objective—The objective is to compare the steady-state rate and extent of absorption of a generic formulation with that of the reference formulation when given as equal labeled doses.

Design—The study design is a multiple-dose, steady-state two-treatment, two-period, two-sequence crossover with an adequate washout period between the two phases of the study. An equal number of subjects should be randomly assigned to the two possible dosing sequences. Before beginning the study, the study protocol should be approved by an institutional review board.

Facilities and Selection of Subjects—See the appropriate section under *Single-Dose Fasting Two-Way Crossover Design*.

Procedure—Extended-release products that are administered once a day should be dosed following an overnight fast of at least 10 hours; subjects should continue fasting for 4 hours postdose. For extended-release products that are dosed every 12 hours (b.i.d.), the morning dose should be given following an overnight fast of about 10 hours, and subjects should continue fasting for 4 hours postdose; the evening dose should be administered 12 hours after the morning dose and after a fast of at least 2 hours and subjects should continue fasting for 2 hours postdose. Each dose should be administered with 240 mL of water.

Restrictions—Study volunteers should observe the following restrictions:

a. No alcohol- or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

b. Subjects should take no Rx medications, including oral contraceptives, beginning two weeks prior to and no OTC medications beginning one week prior to initiation of the study and until after the study is completed.
c. Water may be taken except for 1 hour before and after administration, when no liquid is allowed other than that needed for drug dosing.

Blood Sampling—At least three trough concentrations (C_{min}) on three consecutive days should be determined to ascertain that the subjects are at steady state prior to measurement of rate and extent of absorption after a single-dose administration in a dosing interval at steady state. The three consecutive trough samples should be collected at the same time of the day and should be comparable. For extended-release drug products administered more often than every 24 hours, assessment of trough levels just prior to 2 consecutive doses is not recommended because a difference in the consecutive trough values may occur due to circadian rhythm irrespective of whether or not steady state has been attained. Adequate blood samples should be collected at appropriate times during a dosing interval at steady state to permit estimation of the total area under the concentration-time curve, peak concentration (C_{max}), and time to peak concentration (T_{max}).

Subject Monitoring and Analysis of Blood Samples—See under *Single-Dose Fasting Two-Way Crossover Design*.

Pharmacokinetic Analysis of Data—The following pharmacokinetic data are to be reported for the evaluation of bioequivalence of the generic extended-release product with the reference listed product:

a. Individual and mean blood drug concentration levels
b. Individual and mean trough levels (C_{min})
c. Individual and mean peak levels (C_{max})
d. Calculation of individual and mean steady state $AUC_{interdose}$ are recommended ($AUC_{interdose}$ is AUC during a dosing interval at steady state)
e. Individual and mean percent fluctuation [$= 100 \times (C_{max} - C_{min}) / C_{min}$]
f. Individual and mean time to peak concentration (T_{max})

Statistical Analysis of Pharmacokinetic Data—The log-transformed AUC and C_{max} data should be analyzed statistically using ANOVA. These two parameters for the test product should be shown to be within 80% to 125% of the reference product using the 90% confidence interval. Fluctuation for the test product should be evaluated for comparability with that for the reference product.

Clinical Report, Side Effects, and Adverse Reactions—See under *Single-Dose Fasting Two-Way Crossover Design.*

Single-Dose, Two-Way Crossover Design under Nonfasting Conditions

Objective—The objective is to compare the rate and extent of absorption of a generic formulation with that of the reference-listed formulation under nonfasting conditions when given as equal labeled doses.

Design—The study design is a randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design for studying the effects of food on the BA of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal (fed condition) in the other period. A similar, two-treatment, two-period, two-sequence crossover design is recommended for a fed BE study except that the treatments should consist of both test and reference formulations administered follow-

ing a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BA and fed BE studies.

Selection of Subjects—Both food-effect BA and fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on BA to claim an absence of food effects, or to claim BE in a fed BE. A minimum of 12 subjects should complete the food-effect BA and fed BE studies.

Procedure—Each subject should receive the following two treatments:

Treatment 1: Generic extended-release product administered after a high-fat-content breakfast.

Treatment 2: Innovator extended-release product (reference listed drug) administered after a high-fat-content breakfast.

Following an overnight fast of at least 10 hours, subjects receiving treatments under nonfasting conditions should be served a high-fat breakfast then immediately dosed with Treatment 1 or Treatment 2 with 240 mL of water. No food should be allowed for at least 4 hours postdose, with water allowed after the first hour. Subjects should be served scheduled standardized meals throughout the study, and the same meals should be served during all phases of the study.

Restrictions, Blood Sampling, Subject Monitoring, and Analysis of Blood Samples—For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. Consideration should be given to the possibility that co-administration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

Statistical Analysis of Pharmacokinetic Data—The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect BA and fed BE studies:

- Total exposure, or area under the concentration-time curve ($AUC_{0-\infty}$, AUC_{0-T})
- Peak exposure (C_{max})
- Time to peak exposure (T_{max})
- Lag-time (T_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant pharmacokinetic parameters

For further information on statistical analysis, see *FDA Guidance for Industry—Food Effect Bioavailability and Fed Bioequivalence Studies;* December 2002.

WAIVER OF IN VIVO BIOEQUIVALENCE STUDY REQUIREMENTS

To conserve resources and avoid unnecessary clinical trials, the requirement to demonstrate bioequivalence based on in vivo clinical studies can be waived, based on documentation of BE using in vitro performance tests.

Waiver Based on the Pharmaceutical Dosage Form

A drug product's in vivo comparative bioavailability or bioequivalence may be waived if the products to be compared contain the same active substance(s) in the same concentration, the same excipients in comparable concentrations, and meet one of the following criteria:

(a) aqueous solutions to be administered parenterally;

(b) solutions for oral use that do not contain an excipient that is known or suspected of affecting gastro-intestinal transit or absorption of the active substance;

(c) gases;

(d) powders for reconstitution as a solution;

(e) otic or ophthalmic products prepared as aqueous solutions;

(f) topical products prepared as aqueous solutions; or

(g) inhalation products or nasal sprays, tested to be administered with or without essentially the same device. Special in vitro performance testing should be required to document comparable device performance.

Waiver Based on the Dose

When a single-dose fasting BE study is conducted on the designated (usually highest) strength of the drug product, the requirement to conduct additional in vivo BE studies on the lower strengths of the same product can be waived provided that the lower strength (a) is in the same dosage form, (b) is proportionally similar in its active and inactive ingredients, (c) has the same drug release mechanism as the highest strength, and (d) meets an appropriate in vitro dissolution test. The drug products should exhibit similar dissolution profiles between the strengths, based on an F_2 statistical test value >50.

Waiver Based on the Biopharmaceutical Classification System (BCS)

For all countries, the need to conduct in vivo BE studies for both "similars" (see *Appendix* for U.S. history) and new multisource products can be a significant resource burden. Depending on risk tolerance, a country might rely solely on dissolution (as the U.S. did for nonbioproblem drug products approved prior to 1962) or solely on in vivo studies (as the U.S. did generally for drug products approved after 1962). The BCS is a valid option for replacing in vivo with in vitro studies. It can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., Class 1) formulated in immediate-release solid oral dosage forms that exhibit rapid in vitro dissolution (e.g., 85% dissolved in 30 minutes). The drug products should exhibit similar dissolution profiles, based on an F_2 statistical test value >50. In countries and regions with especially constrained resources, BCS may be extended to the following drug classes: (1) Class 1 drugs if the dosage form exhibits dissolution $\geq$85% in 45 minutes; (2) Class 2 drugs that are soluble at pH 6.8 if the dosage form exhibits dissolution $\geq$85% in 30 minutes; (3) Class 2 drugs that are soluble in surfactant at pH 6.8 if the dosage form exhibits $\geq$85% in 30 minutes; (4) Class 3 drugs if the dosage form exhibits $\geq$85% dissolution at 15 minutes.

APPENDIX

Organizations Cited and Their Web Sites

WHO (World Health Organization)—www.who.ch

ICH (International Conference on Harmonization)—www.ifpma.org/ich1.html

FDA (United States Food and Drug Administration)—www.fda.gov/cder

www.fda.gov/cder/guidance/index.htm (for guidances text)

www.fda.gov/cder/ob/default.htm (for the Orange Book)

USP–NF (United States Pharmacopeia and National Formulary)—www.usp.org

"Similars" in the U.S.

Many nations and regions, including the U.S., have been or are challenged to develop "generic" laws that assure therapeutic equivalence between pioneer products and corresponding multisource products. A brief history of the U.S. in this regard appears below:

- The 1902 federal law required that biologic products such as vaccines be evaluated for "safety, purity, and potency."
- The 1906 Food and Drugs Act added regulation of drugs other than biologics.
- The 1938 Federal Food, Drug and Cosmetic Act created the FDA and required that the new Agency conduct a safety evaluation on drugs prior to marketing on the basis of data submitted in a New Drug Application (NDA).
- The Drug Amendments of 1962 amended the 1938 Act to include an effectiveness requirement for approval of an NDA.
- FDA created the Drug Efficacy Study Implementation (DESI) project to assess the efficacy of new drugs approved between 1938 and 1962.
- Pending conclusion of a DESI finding, FDA permitted marketing of "old, me-too" drug products (as opposed to pre-1938 grandfathered) that were identical, similar, or related to drug products that were undergoing DESI review and that had entered the market between 1938 and 1962.
- Via a 1970 Federal Register Notice published April 24, 1970 (35 F.R. 6574), FDA terminated marketing of "me-too" drug products unless (a) the DESI review had confirmed the safety and efficacy of a corresponding reference product, and (b) the manufacturer of the "me-too" product submitted an Abbreviated New Drug Application (ANDA) that provided information about its formulation and manufacture.
- The Supreme Court in the *United States v. Generix Drug Corporation* concluded that each "me-too" drug product marketed between 1938 and 1962 required an ANDA.
- FDA finalized the 1977 Bioavailability/Bioequivalence (BA/BE) regulations (21 CFR 320) that supported a requirement for BA in NDAs, including DESI-effective new drugs approved between 1938 and 1962, and BE data in ANDAs as part of the safety and efficacy information in an application.
- FDA created the paper NDA policy in 1981 (46 FR 27396, May 19, 1981) to permit approval of generic equivalents of post-1962 new drug products on the basis of literature and product-specific data.
- The U.S. Congress passed the 1984 Waxman-Hatch amendments to the Federal Food, Drug, and Cosmetic Act that created a generic new drug approval system (505(j)) for all new drugs and that terminated the need for a paper NDA policy.

The U.S. law allowing a generic system thus became available in 1984. For any country, including the U.S., the task becomes, with finalization of this type of law, two-fold. First, "similars" already in the marketplace, which may or may not be either pharmaceutically equivalent or bioequivalent, require consideration. Second, new multisource products entering a market after a generic law is passed require documentation of pharmaceutical equivalence and bioequivalence in a regulatory filing.

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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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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Basis for Using Moisture Vapor Transmission Rate per Unit Product in the Evaluation of Moisture-Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms

PQRI Container–Closure Working Group

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ABSTRACT For pharmaceutical solid oral dosage forms, it is well recognized that the most common cause for a packaged product failing to meet its specification is its instability as a result of moisture uptake (*1–3*). The failure is usually related to out-of-specification or out-of-range values in any or combination of the following quality attributes: assay, product degradants, dissolution rate, and other physical properties.

Pharmaceutical solid oral dosage forms are typically packaged in plastic bottles, thermoformed plastic blisters, or cold-formed aluminum blisters. These container–closure systems are sealed either by compression fit between a hard surface and a soft surface or by application of heat to an adhesive layer of polymers. These container–closure systems are considered semipermeable packages, and therefore the moisture-barrier properties need to be characterized. For the purposes of this discussion, it is assumed that manufacturers have procedures in place to demonstrate that container–closure systems are free from pinholes and channels. Therefore, packages with pinholes or channels that allow convective mass transfer are excluded.

Change from the use of one container–closure system to another requires demonstrating that the container–closure system affords equivalent or better protection. This can be achieved in one of two ways: either by generating formal stability data or by providing performance-based data for the container–closure system being compared. We will show that the relationship of a container–closure system's moisture vapor transmission rate (MVTR) and the number of units contained in the system can be used to demonstrate moisture-barrier equivalence. Specifically, it will be shown that MVTR/Unit Product is the critical parameter for demonstrating this equivalence.

INGRESS OF MOISTURE TO CONTAINER–CLOSURE SYSTEMS

Moisture ingress into well-sealed primary packages occurs via two major routes: permeation through the container wall and the seal layer, or diffusion through narrow imperfection channels in the seal or the container wall. Note that other than imperfections introduced in the forming and sealing operations, the container wall is either a nonporous dense polymer or a multilayer polymer/aluminum foil composite.

Gas permeation through polymers has long been recognized to follow a solution-diffusion mechanism[a] and can be quantitatively described by Fick's law. When the moisture partial pressures on both sides of the barrier are held constant, steady-state permeation will be reached in due time.[b] At steady state, the following relationship holds for a flat film:

Steady-state Moisture Permeation Rate, MPR = (permeability coefficient, P_p) × (surface area for permeation, A_p) × (moisture partial pressure difference across the polymer per unit film thickness, $\Delta p / l$),

or, expressed mathematically,

$$MPR = P_p \times A_p \times \frac{\Delta p}{\ell} \quad [1]$$

The moisture permeability coefficient, P_p, of a moisture-barrier or seal polymer (such as HDPE,[c] PVC, PVDC, PCTFE, LDPE, PP, polycycloolefins, PET, and various copolymers) is a characteristic property of the individual barrier material. It is practically a constant for a given material at a given temperature, essentially independent of the driving force, Δp.

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[a] The gas molecules are first "absorbed" into one face of the polymer barrier, then move through the bulk of the polymer by molecular diffusion, and finally are "desorbed" from the other face of the polymer barrier. Polymers with low affinity for water molecules, and/or with low free volume and/or strong chain–chain attraction, are therefore high water barriers.

[b] The time to reach steady state depends primarily on the diffusion coefficient and the thickness of the barrier. (See, for example, J. Crank and G.S. Park, *Diffusion in Polymers,* Academic Press, New York 1968.)

[c] See Glossary of Acronyms.

For a specified commercial container, Equation (1) has to be integrated over the whole effective permeation area, where the thickness may be variable, in order to determine the overall steady-state moisture permeation rate, *MPR,* into the container:

$$MPR = (P_p \times \oint \frac{dA_p}{\ell}) \times \Delta p \quad [2]$$

Note that the term in the parenthesis in Equation (2),

$$(P_p \times \oint \frac{dA_p}{\ell}),$$

is a property of the specific container of interest.

Diffusion of gases through microchannels is nonconvective and is also well described by Fick's law, and it can be described by an expression similar to Equation (1). For a given sealed container, the following equation applies:

Steady-State Moisture Diffusion Rate, *MDR* = (effective permeability coefficient, P_d) × (effective surface area for diffusion, A_d) × (moisture partial pressure difference across the container, Δp) / (effective diffusion length, l_d) or, expressed mathematically,

$$MDR = (P_d \times \frac{A_d}{\ell_d}) \times \Delta p \quad [3]$$

Note that the term

$$(P_d \times \frac{A_d}{\ell_d})$$

is also a property of the specific sealed container of interest. In the absence of gross defects, overall (steady-state) moisture vapor transmission rate, *MVTR,* into a given sealed container is thus the combined contribution of the two moisture ingress routes:

$$MVTR = MPR + MDR$$

$$= (P_p \times \oint \frac{dA_p}{\ell}) \times \Delta p + (P_d \times \frac{d}{\ell_d}) \times \Delta p \quad [4]$$

$$= K \times \Delta p$$

where K is a characteristic property of the specific container–closure system of interest. The unit for MVTR is typically expressed as mg/day/container; the water partial pressure is often expressed in mmHg.

Equation (4) embodies the theoretical basis for quantifying the moisture-barrier property of a given container at a given temperature. It also provides the foundation for experimental determination of this intrinsic property of a given container–closure system.

Experimentally, a sufficient amount of high-capacity desiccant is placed in the empty container. The container is sealed with the selected closure, placed in an environmental chamber at fixed temperature and relative humidity, and the weight gain is monitored with time. If the amount and type of desiccant are chosen correctly, the internal water partial pressure will remain low (e.g., <5 mmHg at 40 °C) throughout the measurement run; as a result, the Δp in Equation (4) remains essentially constant during the course of the MVTR measurement.

MVTR is, therefore, interchangeable with *K,* the characteristic moisture barrier of a given container–closure system via the rearranged Equation (4):

$$K = \frac{MVTR}{(\Delta p)_{test}} \quad [4a]$$

where $(\Delta p)_{test}$ is a constant depending only on the test condition.

In the following discussion, mass-balance considerations together with Equation (4a) will be used to establish the equation that governs the moisture–time profile inside any container–closure system for solid oral dosage forms. The governing equation (see below) unequivocally describes the time profile of the moisture content or relative humidity inside the container for a given set of external test conditions (e.g., ICH 40 °C/75% RH or 30 °C/65% RH or 25 °C/60%

RH). Using the governing equation, we will proceed to demonstrate that

equivalent value of (MVTR/unit product) corresponds to equivalent moisture protection.

GOVERNING EQUATION

Consider the mass balance for water within a sealed container. Assuming negligible chemical consumption of water, we can write the following mass-balance equation with the help of Equation (4) for a sealed package[d]:

$$\frac{dn}{dt} = MVTR = K \times (p_{ex} - p) \quad [5]$$

where n is the total mass of water inside the container, in the headspace and solid (mg)
t is time (day)
p is the (internal) headspace partial pressure of water vapor (mmHg)
p_{ex} is the external partial pressure of water vapor (mmHg).

The total mass of water inside the container, n, comprises the moisture in the headspace and in the solids. The solid could be the product, the desiccant, or fillers such as cotton.

Let the total headspace volume inside the container be V (mL); then the rate of change of water mass in the headspace, according to the ideal gas law, will be

$$\frac{dn_{(headspace)}}{dt} = 18\frac{V}{RT}\frac{dp}{dt} \quad [5a]^{e}$$

If there are N solid components that absorb water vapor reversibly inside the container, the rate of change of water mass in the solids will be

$$\frac{dn_{(solids)}}{dt} = \sum_{1}^{N} m_i \frac{dC_i}{dt} \quad [5b]$$

where m_i is the dry mass of component i inside the container (g)
C_i is the equilibrium concentration of water in component i (mg/g dry basis) when the water partial pressure inside the container is p (mmHg)
R is the gas constant (62.36 mmHg-mL/mmole-°K)
T is the temperature (°K)
t is time (days).

Equation (5) can now be rewritten as

$$18\frac{V}{RT}\frac{dp}{dt} + \sum_{1}^{N} m_i \frac{dC_i}{dt} = K \times (p_{ext} - p) \quad [6]$$

Integration of Equation (6) gives[f]:

$$\left[\frac{18V}{RT}\int_{p_0}^{p_f}\frac{dp}{p_{ext} - p} + \sum_{1}^{N} m_i \int_{C_i^0}^{C_i^f}\frac{dC_i}{p_{ext} - p}\right] \times \frac{1}{K} = t \quad [7]$$

where p_0 is the initial water partial pressure inside the container
p_f is the water partial pressure at time t
C^0_i is the initial equilibrium water content of component i
C^f_i is the equilibrium water content of component i at time t.

The first term in Equation (7),

$$\frac{18V}{RT}\int_{p_0}^{p_f}\frac{dp}{p_{ext} - p},$$

corresponds to the total change in water content of the headspace, and the second term,

[d] For the vast majority of oral solid dosage forms, the amount of water consumed by chemical reaction is negligibly small or nonexistent. The impact of the small induction period on this mass-balance equation is negligible because of the long time scale of shelf-life stability studies (2 years for most oral solid products).

[e] The number 18, the molecular mass of water, was included to ensure dimensional consistency.

[f] Implicit in this mathematical operation is the assumption that the headspace and the various solid contents in the container are at thermodynamic equilibrium at any given instant. This turns out to be a very good approximation as demonstrated by the data shown in *Appendix A*. In those examples, three different products were preequilibrated at preselected conditions and were sealed with desiccant in glass vials separately. The headspace relative humidity was then monitored over time to determine how fast the system reached equilibrium. The data clearly demonstrated that it took no more than one day, which is negligible compared with the typical expectation of 2-yr shelf life. The equilibrium approximation is thus well justified.

$$\sum_{1}^{N} m_i \int_{C_i^0}^{C_i^f} \frac{dC_i}{p_{ext} - p},$$

corresponds to total change in water content of the various solids in the container.

For the vast majority of packages for solid dosage forms, the first term is negligibly small relative to the second term. This can be demonstrated by simply considering the amount of water that can be held in the (gaseous) container headspace and in the solids.

For example, consider the change in the amount of water in one mL of headspace gas (air) at 40 °C[g] when the RH increases from 15% to 75%, an extreme change for a primary package. This corresponds to a change of 0.031 mg water per mL of headspace. For a 100-mg tablet packaged in a unit-dose blister, the typical headspace is no more than 1.0 mL. Thus, even if the headspace has increased from 15% to 75%, the amount of water in the headspace will increase by 0.03 mg, which corresponds to a mere 0.03% of the mass of the 100-mg tablet.

For a multiple-unit container such as a 75-mL bottle containing 30 × 100 mg tablets, the extreme change of headspace humidity of 60% shown above corresponds to 2.32 mg water. This amounts to only 0.08% of the total mass of the tablet, which is near or below the accuracy of the current methods used for water content determination.

Equation (7) can therefore be simplified to the following expression with negligible loss in accuracy[h]:

$$\sum_{1}^{N} m_i \int_{C_i^0}^{C_i^f} \frac{dC_i}{p_{ext} - p} = K \times t = \frac{MVTR}{(\Delta p)_{test}} \times t \quad [8]$$

This expression is the governing equation that describes the water content of component *i* as a function of time under any of the ICH stability testing conditions. The relationship between C_i and p is an intrinsic material property, typically expressed in terms of "moisture sorption isotherm" that can be determined experimentally and independently for each solid.

The definitions for the symbols in Equation (8) are presented below again for clarity:

t	is the duration of the test time
m_i	is the dry mass of component *i* in the container
p	is the water partial pressure inside the container
p_{ext}	is the constant external water partial pressure (e.g., 55.3 mmHg × 75% at 40 °C, corresponding to the 40 °C/75% RH test condition)
C^0_i	is the initial equilibrium water content of component *i*
C^f_i	is the equilibrium water content of component *i* at time *t*
$(\Delta p)_{test}$	is a constant depending only on the test condition used in determining *MVTR* at the temperature of interest
MVTR	is the steady-state moisture transmission rate into the container/closure at the temperature of interest and the relative humidity in the testing chamber

IMPLICATION OF THE GOVERNING EQUATION

The utility of Equation (8) in establishing moisture-barrier equivalence can be illustrated by considering a simple case in which no other moisture-absorbing solid is present other than the drug product itself. This simplified case corresponds to, for example, single-unit blister packages or multiple-unit bottle packages without desiccant; the equation simplifies to:

$$\int_{C_1^0}^{C_1^f} \frac{dC_1}{p_{ext} - p} = \frac{MVTR}{m_i} \times \frac{1}{(\Delta p)_{test}} \times t \quad [9]$$

where m_1 is the mass of the drug product itself.

Note that the only unknown in Equation (9) is (C^f_1), the final moisture content of the drug product at time *t* for a packaged product under stability testing.

Thus, for a given drug product of the same initial moisture content, as long as the value ($MVTR/m_1$) is kept constant, the moisture content of the drug product will be the same at any specified time point during the stability test, regardless of the primary container.

In other words, two container–closure systems that exhibit the same (MVTR/unit product) are equivalent as far as moisture protection is concerned.

An example is given in *Appendix C* to illustrate and support this conclusion.

Another example is given in *Appendix D* to illustrate the effectiveness of the approach for differentiating the degree of moisture protection offered by different container–closure systems.

[g] The water vapor pressure at 40 °C is 55.3 mmHg.

[h] The conclusion drawn from this simplification is not changed even if the headspace contribution is not negligible. This simplification is made here mainly to make the mathematical presentation as simple as possible. See *Appendix B* for details.

CONCLUSION AND RECOMMENDATIONS

In this article, we have presented a step-by-step derivation of the equation that governs the time profile of the moisture content inside any container–closure system for solid oral dosage forms. The physical phenomena involved are straightforward and can be reduced to rigorous mathematical treatment with a high degree of accuracy. As clearly illustrated in the discussion associated with Equation (9), (MVTR/unit product) is indeed the critical container–closure parameter that allows one to establish the moisture-barrier equivalence.

On the practical side, the MVTR determination is subject to experimental errors as well as small variations in the properties of the container–closure, such as wall thickness and closure sealing. In practice, an equivalent (MVTR/unit product) range must be demonstrated via stability studies or other scientific means for a given drug product during pharmaceutical development. Once this range is established, postapproval changes made to the container–closure system will be assured of moisture-barrier equivalence as long as the (MVTR/unit product) of the modified or new system falls within the qualified range.

Current methods for determination of MVTR may not be sensitive enough for high-barrier materials required for the packaging of moisture-sensitive products. In order to apply the MVTR/unit product concept to high-barrier materials, a method with increased sensitivity is required. An improved test method will thus be investigated as part of the proposed project.

APPENDIX A.

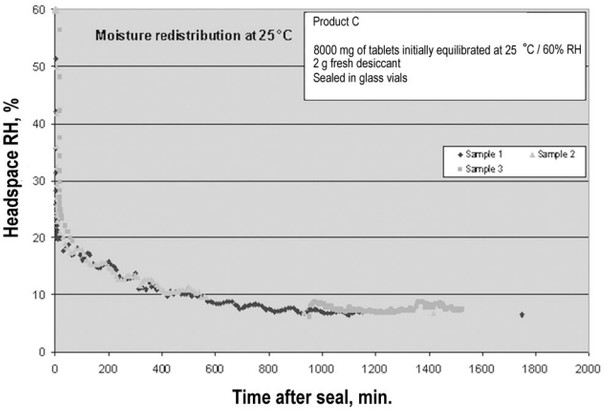


Fig. 1. Rate of moisture exchange

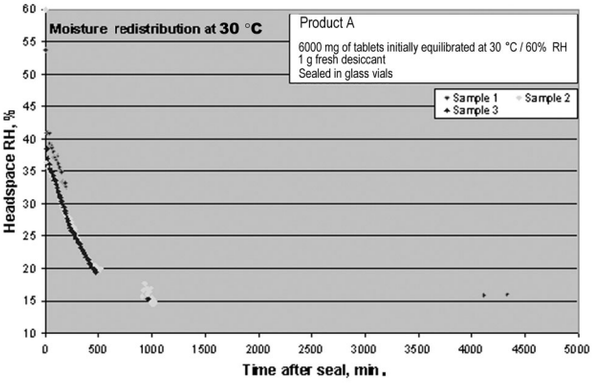


Fig. 2. Rate of moisture exchange

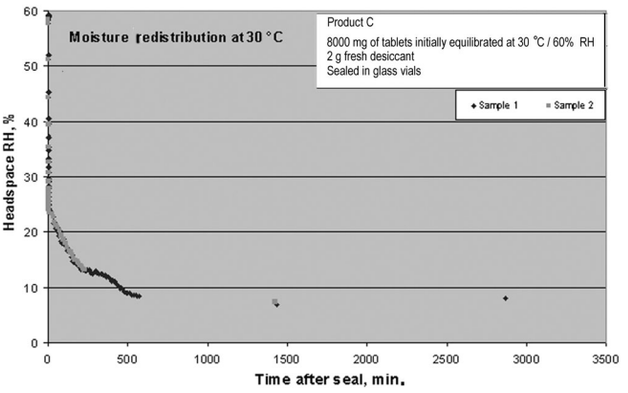


Fig. 3. Rate of moisture exchange

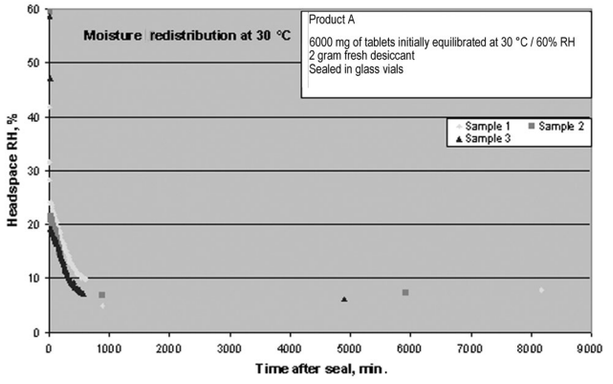


Fig. 4. Rate of moisture exchange

APPENDIX B.

Moisture-barrier equivalence when headspace contribution is not negligible

In instances when one packages a small quantity of product in an oversized container, for example one tablet in an 80-mL bottle, Equation (7) is simplified to:

$$\frac{18}{RT}\times\frac{V}{m_i}\int_{p_0}^{p_f}\frac{dp}{p_{est}-p}+\int_{C_1^0}^{C_1^f}\frac{dC_1}{p_{est}-p}=\frac{MVTR}{m_1}\times\frac{1}{(\Delta p)_{test}}\times t \quad [10]$$

Equation (10) is the governing equation for a container–closure system without desiccant when the water content in the headspace is of the same order of magnitude as that in the product. (See the examples preceding Equation (8) for this estimation.)

In this case, two container–closure systems are equivalent as long as ($MVTR/m_1$) and (V/m_1) are the same. In other words, when the headspace contribution is not negligible, the ‘‘headspace volume per product mass’’ together with ‘‘MVTR per product mass’’ can be used to establish moisture-barrier equivalence between container systems. The validity of ‘‘MVTR/Unit Product’’ thus holds.

APPENDIX C.

Examples of moisture-barrier equivalency for container–closure systems that exhibit the same (MVTR/unit product)

In this example, Product B was packaged in two different blister types and two different bottle configurations. The packages were chosen so that the ($MVTR/m_1$) values for Bottle (7 tablets) and Blister 1 are similar. The same situation holds for Bottle (30 tablets) and Blister 2. The packages were stored in an ICH 40 °C/75% RH chamber for 180 days. At different times in the test period, individual packages were taken from the chamber and water activity in the product was determined.[i]

The data clearly demonstrate that the water activity profile (vs. time) of the product indeed is the same when the ($MVTR/m_1$) value of the container–closure system is adjusted to the same level.[j] In other words, Bottle (7 tablets) and Blister 1 and Bottle (30 tablets) and Blister 2, respectively, are equivalent as far as moisture barrier is concerned.

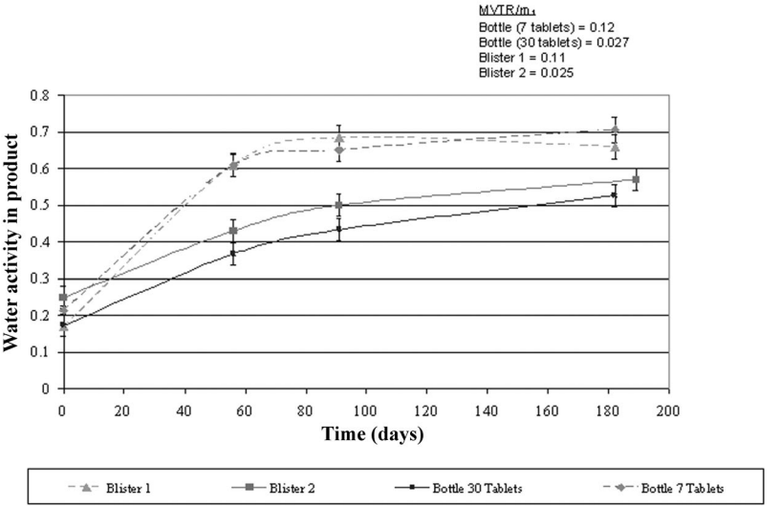


Fig. 5. Product B in different packages

APPENDIX D.

Evaluation of the moisture-protection efficiency of packaging using (MVTR/unit product) for solid oral dosage forms

This example illustrates the use of (MVTR/unit product) to evaluate the protection efficiency of containers. The data are from an isolated study conducted by a participating company. A lower (MVTR/unit product) resulted in lower product moisture content and hence better protection of the product from moisture. Product X was sealed in HDPE bottles A and B and stored in at 25 °C/60% RH. MVTR for the bottles was measured under the same conditions using steady-state data. The MVTR values were 0.282 and 0.342 mg/day/bottle for Bottles A and B, respectively. The packaging configurations and the *MVTR/m* values (where *m* is the number of dose units in the bottles) were:

(1) 10 tablets of X in bottle A, MVTR/mL = 0.0282 mg/day/tablet
(2) 20 tablets of X in bottle B, MVTR/mL = 0.0171 mg/day/tablet.

The increase in the rate of moisture uptake by tablets in bottle A using B as a reference was calculated to be: $R = 0.0282/0.0171 = 1.65$, and it was thus expected that bottle B would provide a better moisture protection for product X than bottle A.

At different times, samples were removed from the stability chamber, and the product water content was determined by an LOD method.

[i] Because the packages were not prepared under exactly the same environment and at exactly the same time, the initial water activity did vary somewhat; nevertheless, they are in the same range at approximately 0.23. A variety of instruments commonly used in areas such as the food industry and based on principles of dew-point or capacitance could be used for the water-activity measurement.

[j] The slight difference between Blister 2 and Bottle (30 Tablets) is due to the small difference in the "initial" water activity.

The observed rates of product water content increased in bottle A relative to bottle B were 1.60, 1.68, and 1.50 at 3, 5, and 9 months, respectively. These results agree very well with the theoretical value of 1.65 for the two bottles and thus show that (MVTR/unit product) is an effective criterion for evaluating the moisture protection efficiency of primary packages and that equivalent protection can be achieved by proper design of the *MVTR/m* value using different containers for solid dosage forms.

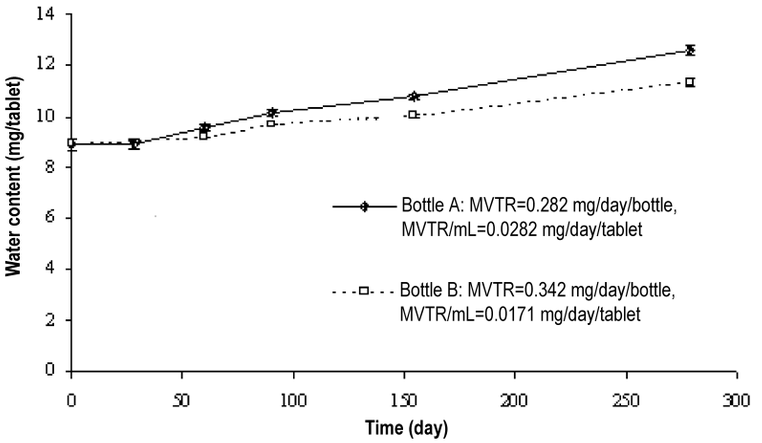


Fig. 6. MVTR/unit and waater content of Product X HDPE bottles at 25 °C/60% RH

GLOSSARY OF ACRONYMS

HDPE	high-density polyethylene
LDPE	low-density polyethylene
MDR	overall steady-state moisture diffusion rate, Equation (3)
MPR	overall steady-state moisture permeation rate, Equation (2)
MVTR	overall moisture vapor transmission rate, Equation (4)
PET	poly(ethylene terephthalate)
PP	polypropylene
PVC	poly(vinyl chloride)
PVDC	poly(vinylidene chloride)
PCTFE	poly(chlorotrifluoro ethylene)

REFERENCES

1. FDA Guidance for Industry, *Container–Closure Systems for Packaging Human Drugs and Biologics*, Section III G, "Solid Oral Dosage Forms and Powders for Reconstitution," May 1999, 33.
2. S.I.F. Badawy, A.J. Gawronski, and F.J. Alvarez. Application of sorption-desorption moisture transfer modeling to the study of chemical stability of a moisture-sensitive drug product in different packaging configurations. *Int J Pharm.* 2001;223:1–13.
3. C. Ahlneck and G. Zografi. The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. *Int J Pharm.* 1990;62:87–95.

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
2004 USP DICTIONARY SUPPLEMENT 5

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2004 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2004) 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.

Amustaline Dihydrochloride [*2004*] (aye mus′ ta leen). $C_{22}H_{25}Cl_2N_3O_2.H_2O$. 507.28. (1) β-Alanine, *N*-9-acridinyl-, 2-[bis(2-chloroethyl)amino]ethyl ester, dihydrochloride; (2) 2-[Bis(2-chloroethyl)amino]ethyl 3-(acridin-9-ylamino)propanoate dihydrochloride. *CAS-210584-54-6. Ex-vivo blood bank process for inactivation of viruses, bacteria, parasites, and leukocytes in red blood cells* (*nucleic acid alkylator*). (Cerus) ✧*S-303ôñ2HCl*

MGVRHPPCSH RLLAVCALVS LATAALLGHI LLHDFLLVPR ELSGSSPVLE
ETHPAHQQGA SRPGPRDAQA HPGRPRAVPT QCDVPPNSRF DCAPDKAITQ
EQCEARGCCY IPAKQGLQGA QMGQPWCFFP PSYPSYKLEN* LSSSEMGYTA
TLTRTTPTFF PKDILTLRLD VMMETENRLH FTIKDPANRR YEVPLETPRV
HSRAPSPLYS VEFSEEPFGV IVHRQLDGRV LLNTTVAPLF FADQFLQLST
SLPSQYITGL AEHLSPLMLS TSWTRITLWN RDLAPTPGAN LYGSHPFYLA
LEDGGSAHGV FLLNSNAMDV VLQPSPALSW RSTGGILDVY IFLGPEPKSV
VQQYLDVVGY PFMPPYWGLG FHLCRWGYSS TAITRQVVEN* MTRAHFPLDV
QWNDLDYMDS RRDFTFNKDG FRDFPAMVQE LHQGGRRYMM IVDPAISSSG
PAGSYRPYDE GLRRGVFITN ETGQPLIGKV WPGSTAFPDF TNPTALAWWE
DMVAEFHDQV PFDGMWIDMN EPSNFIRGSE DGCPNNELEN PPYVPGVVGG
TLQAATICAS SHQFLSTHYN LHNLYGLTEA IASHRALVKA RGTRPFVISR
STFAGHGRYA GHWTGDVWSS WEQLASSVPE ILQFNLLGVP LVGADVCGFL
GNTSEELCVR* WTQLGAFYPF MRNHNSLLSL PQEPYSFSEP AQQAMRKALT
LRYALLPHLY TLFHQAHVAG ETVARPLFLE FPKDSSTWTV DHQLLWGEAL
LITPVLQAGK AEVTGYFPLG TWYDLQTVPI EALGSLPPPP AAPREPAIHS
EGQWVTLPAP LDTINVHLRA GYIIPLQGPG LTTTESRQQP* MALAVALTKG
GEARGELFWD DGESLEVLER GAYTQVIFLA RNNTIVNELV RVTSEGAGLQ
LQKVTVLGVA TAPQQVLSNG VPVSNFTYSP* DTKVLDICVS LLMGEQFLVS
WC

* - glycosylation sites

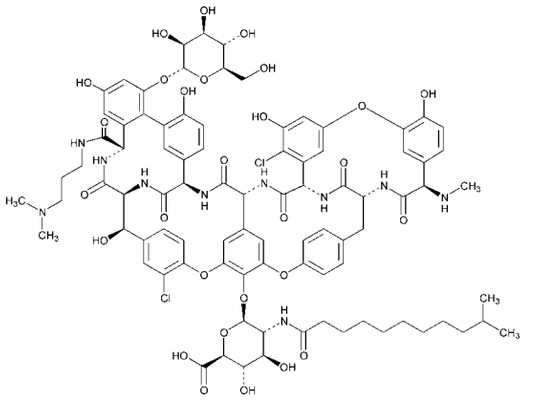
Armodafinil [*2004*] (ar moe daf′ in il). $C_{15}H_{15}NO_2S$. 273.40. (1) Acetamide, 2-[(diphenylmethyl)sulfinyl]-, (–)-; (2) (–)-2-[(*R*)-(Diphenylmethyl)sulfinyl]acetamide. *CAS-112111-43-0*. INN. *Wakefulness promoting agent.* (Cephalon) ✧*CEP-10953*

Carvedilol Phosphate [*2004*] (kar′ ve dil ole). $C_{24}H_{26}N_2O_4.H_3O_4P.½H_2O$. 513.50. (1) 2-Propanol, 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, phosphate (salt), hydrate (2:2:1); (2) (2*RS*)-1-(9*H*-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol phosphate salt (1:1) hemihydrate. *CAS-610309-89-2. Treatment of congestive heart failure, left ventricular dysfunction following myocardial infarction, and management of hypertension.* (GlaxoSmithKline) ✧*SK&F-105517-D*

Cinacalcet [*2004*] (sin a kal′ set). $C_{22}H_{22}F_3N$. 357.42. (1) 1-Naphthalenemethanamine, α-methyl-*N*-[3-[3-(trifluoromethyl)phenyl]propyl]-, (α*R*)-; (2) *N*-[(1*R*)-1-(Naphthalen-1-yl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine.*CAS-226256-56-0. Treatment of hyperparathyroidism and related disorders, such as hypercalcemia* (*reduction of PTH secretion through modulation of calcium ion receptors on parathyroid cells*). Sensipar (Amgen) ✧*AMG073*

Corticorelin Acetate [*2004*] (kor″ ti koe rel′ in). $C_{208}H_{344}N_{60}O_{63}S_2$. 4757.00. (1) Corticotropin-releasing factor (human); (2) Human corticotropin-releasing factor. *CAS-86784-80-7. Treatment of symptoms associated with peritumoral edema in brain tumor patients.* Xerecept (Hollister-Stier) *[Note—The source of the product* (*human, porcine, etc.*) *must be indicated in the labeling.]* ✧*NEU 3002*

Dalbavancin [*2004*] (dal ba van′ sin). $C_{88}H_{100}Cl_2N_{10}O_{28}$. 1816.69. (1) Ristomycin A aglycone, 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-*O*-[2-deoxy-2-[(10-methyl-1-oxoundecyl)amino]-β-D-glucopyranuronosyl]-38-[[[3-(dimethylamino)propyl]amino]carbonyl]-42-*O*-α-D-mannopyranosyl-N^{15}-methyl-; (2) 2-Deoxy-1-*O*-[(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50a*R*)-5,31-dichloro-38-[[3-(dimethylamino)propyl]carbamoyl]-6,11,34,40,44-pentahydroxy-42-(α-D-mannopyranosyloxy)-15-(methylamino)-2,16,36,50,51,59-hexaoxo-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-1*H*,15*H*-4,8:10,14:25,28:43,47-tetrametheno-34*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosin-56-yl]-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronic acid (main component). *CAS-171500-79-1*. INN. *Antibiotic.* (Aventis) ✧*BI397; MDL 64,397; A-A-1; VER001*



Darifenacin Hydrobromide [*2004*] (dar ee fen′ a sin). $C_{28}H_{30}N_2O_2$.HBr. 507.50. [Darifenacin is INN and BAN.] (1) 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, monohydrobromide, (3*S*)-; (2) (*S*)-2-{1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidnyl}-2,2-diphenylacetamide hydrobromide. *CAS-133099-07-7; CAS-133099-04-4* [darifenacin]. *Treatment for an overactive bladder.* Enablex (Novartis) ✧*UK-88525-04* (*hydrobromide*)

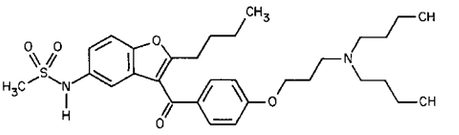
Dasantafil [*2004*] (da san′ ta fil). $C_{22}H_{28}BrN_5O_5$. 522.40. (1) 1*H*-Purine-2,6-dione, 7-[(3-bromo-4-methoxyphenyl)methyl]-1-ethyl-3,7-dihydro-8-[[(1*R*,2*R*)-2-hydroxycyclopentyl]amino]-3-(2-hydroxyethyl); (2) 7-(3-Bromo-4-methoxybenzyl)-1-ethyl-8-[[(1*R*,2*R*)-2-hydroxycyclopentyl]amino]-3-(2-hydroxyethyl)-3,7-dihydro-1*H*-purine-2,6-dione. *CAS-569351-91-3*. INN. *Treatment of erectile dysfunction* (*phosphodiesterase* (*PDE*) *5 isoenzyme inhibitor*). (Schering-Plough) ✧*SCH 446132*

Denufosol Tetrasodium [*2004*] (den ue foe′ sol). $C_{18}H_{23}N_5Na_4O_{21}P_4$. 861.30. [Denufosol is INN.] (1) Uridine 5′-(pentahydrogen tetraphosphate), P′′′→5′-ester with 2′-deoxycytidine, tetrasodium salt; (2) 2′-Deoxycytidine(5′)tetraphospho(5′)uridine tetrasodium salt. *CAS-318250-11-2; CAS-211448-85-0* [denufosol]. *Treatment of rhinitis, URI and lung disease, cystic fibrosis, retinal detachment and edema.* (Yamasa) ✧*INS37217*

Depelestat [*2004*] (dep el′ e stat). $C_{282}H_{412}N_{74}O_{75}S_6$. 6231.00. (1) Proteinase inhibitor M/NEI (synthetic human); (2) Human recombinant neutrophil elastase inhibitor, homologue of the second Kunitz domain of Inter-alpha-trypsin inhibitor light chain: [Glu285,Ile297,Phe300,Pro301,Arg302]AMBP protein precursor-(285-340)-peptide (human). *CAS-506433-25-6*. INN. *Treatment of bronchopulmonary inflammatory damage, specifically Cystic Fibrosis.* (Avecia) ✧*DX-890*

Dirlotapide [*2004*] (dir loe ta ′ pide). $C_{40}H_{33}F_3N_4O_3$. 674.70. (1) 1*H*-Indole-2-carboxamide, 1-methyl-*N*-[(1*S*)-2-[methyl(phenylmethyl)amino]-2-oxo-1-phenylethyl]-5-[[[4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl]carbonyl]amino]-; (2) *N*-[(1*S*)-2-(Benzylmethylamino)-2-oxo-1-phenylethyl]-1-methyl-5-[[[4′-(trifluoromethyl)biphenyl-2-yl]carbonyl]amino]-1*H*-indole-2-carboxamide. *CAS-481658-94-0*. INN. *Treatment of obesity in companion animals* (*dogs*)(*gut microsomal triglyceride transport protein* (*gMTP*) *inhibitor*). (Pfizer) ✧*CP-742,033*

Dronedarone Hydrochloride [*2004*] (droe ne′ da rone). $C_{31}H_{44}N_2O_5S$.HCl. 593.20. [Dronedarone is INN.] (1) Methanesulfonamide, *N*-[2-butyl-3-[4-[3-(dibutylamino)propoxy]benzoyl]-5-benzofuranyl]-, monohydrochloride; (2) *N*-[2-Butyl-3-[*p*-[3-(dibutylamino)proproxy]benzoyl]-5-benzofuranyl] methanesulfonamide-, monohydrochloride. *CAS-141625-93-6; CAS-141626-36-0* [dronedarone]. *Antiarrhythmic.* (Sanofi-Synthelabo) ✧*SR33598B*



Edratide [*2004*] (er′ ra tide). $C_{111}H_{149}N_{27}O_{28}$. L-Glycyl-L-tyrosyl-L-tyrosyl- L-tryptophyl-L-seryl-L-tryptophyl-L-isoleucyl-L-arginyl-L-glutaminyl-L-prolyl-L-prolyl-L-glycyl-L-lysyl-L-glycyl-L-glutamyl-L-glutamyl-L-tryptophyl-L-isoleucyl-L-glycine. *CAS-433922-67-9*. INN. *Treatment of systemic lupus erythematosus.* (Teva, Israel) ✧*TV-4710*

Eglumetad [*2004*] (ee gloo′ me tad). $C_8H_{11}NO_4$. 185.20. (1) Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-, (1*S*,2*S*,5*R*,6*S*)-; (2) (+)-(1*S*,2*S*,5*R*,6*S*)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid. *CAS-209216-09-1; CAS-176199-48-7* [anhydrous]. INN. *Treatment of general anxiety disorders and smoking cessation* (*metabotropic glutamate agonist*). (Lilly) *[Name previously used: Eglumegad.]* ✧*LY354740*

Fidexaban [*2004*] (fye dex′ a ban). $C_{25}H_{24}F_2N_6O_5$. 526.49. (1) Glycine, *N*-[2-[5-(aminoiminomethyl)-2-hydroxyphenoxy]-6-[3-(4,5-dihydro-1-methyl-1*H*-imidazol-2-yl)phenoxy]-3,5-difluoro-4-pyridinyl]-*N*-methyl-; (2) [[2-(5-Carbamimidoyl-2-hydroxyphenoxy)-3,5-difluoro-6-[3-(1-methyl-4,5-dihydro-1*H*-imidazol-2-yl)phenoxy]pyridin-4-yl]methylamino]acetic acid. *CAS-183305-24-0*. INN. *Anticoagulant* (*Factor Xa inhibitor*). (Schering A.G., Germany) ✧*ZK 807834*

Forodesine Hydrochloride [*2004*] (fore oh′ de seen). $C_{11}H_{14}N_4O_4$.HCl. 302.70. (1) 4*H*-Pyrrolo[3,2-*d*]pyrimidin-4-one, 7-[(2*S*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)-2-pyrrolidinyl]-1,5-dihydro-, monohydrochloride; (2) (–)-7-[(2*S*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-yl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one monohydrochloride. *CAS-284490-13-7*. *Treatment of T-Cell malignancies such as acute lymphoblastic leukemia* (*ALL*) *and cutaneous T-cell lymphoma* (*CTCL*). (BioCryst) ✧*BCX-1777*

Gadoxetate Disodium [*2004*] (gad ox′ e tate). $C_{23}H_{28}GdN_3Na_2O_{11}$. 725.72. (1) Gadolinate(2-), [*N*-[2-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]-3-(4-ethoxyphenyl)propyl]-*N*-[2-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]ethyl]glycinato(5-)-κ*N*,κ*O*]-, disodium, [SA-8-11252634-(*S*)]-; (2) Disodium [*N*-[(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]gadolinate(2-).*CAS-135326-22-6*. *Paramagnetic*

Nomenclature

contrast agent for enhancement in magnetic resonance imaging (*MRI*). (Schering Aktiengesellschaft, Germany) ✧*ZK 139834*

Gantacurium Chloride [*2004*] (gan ta kure′ ee um). $C_{53}H_{69}Cl_3N_2O_{14}$. 1-64.50. (1) Isoquinolinium, 2-[3-[[(2*Z*)-2-chloro-1,4-dioxo-4-[3-[(1*S*,2*R*)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)isoquinolinio]propoxy]-2-butenyl]oxy]propyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-, dichloride, (1*R*,2*S*)-; (2) (1*R*,2*S*)-2-[3-[[(2*Z*)-2-Chloro-4-[3-[(1*S*,2*R*)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolinio]propoxy]-4-oxobut-2-enoyl]oxy]propyl]-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolinium dichloride. *CAS-213998-46-0*. INN. *Induces muscle paralysis as a surgical adjunct* (*neuromuscular blocker*). (Cedarburg) ✧*GW-280430A*

Golimumab [*2004*] (goe li mue′ mab). $C_{6530}H_{10068}N_{1752}O_{2026}S_{44}$. Immunoglobulin G1, anti-(human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ-chain, dimer. Molecular weight is approximately 147,000 daltons. *CAS-476181-74-5*. INN. *Treatment of inflammatory disorders; rheumatoid arthritis, uveitis, asthma and Crohn's disease.* (Centocor) ✧*CNTO 148*

Hyaluronidase [*2004*] (hye al ur on′ i dase). **USP** [Injection]. $C_{2600}H_{4040}N_{696}O_{774}S_{23}$ (peptide). 58,170 daltons. (1) Hyaluronidase (sheep testis isoenzyme); (2) Hyaluronidase (glycoprotein, sheep testis isoenzyme). *CAS-488712-31-8; CAS-9001-54-1*. INN; BAN; JAN. *Clearance of vitreous hemorrhage.* Diffusin (Ortho Pharmaceutical†); Enzodase (Bristol-Myers Squibb†); Hyazyme (Abbott†); Vitrase (Biozyme Laboratories Ltd., UK); Wydase (Wyeth-Ayerst) *[Note—The source of the product* (*ovine, porcine, etc.*) *must be indicated in the labeling.]* ✧*HYO6A*
USP DI Category: Spreading agent.

Idronoxil [*2004*] (id roe nox′ il). $C_{15}H_{12}O_3$. 240.25. (1) 2*H*-1-Benzopyran-7-ol, 3-(4-hydroxyphenyl)-; (2) 3-(4-Hydroxyphenyl)-2*H*-chromen-7-ol. *CAS-81267-65-4*. INN. *Antineoplastic which acts as an antiproliferative, topoisomerase II inhibitor; 5α reductase inhibitor.* (Novogen) *[Note—The trivial name, phenoxodiol, has appeared in the literature.]* ✧*NV-06*

Ismomultin Alfa [*2004*] (iz″ moe mul′ tin). $C_{1827}H_{2785}N_{493}O_{530}S_{11}$. 40,489. (1) Glycoprotein gp 39 (human cartilage isoform Org 39141); (2) 47-261-Glycoprotein gp 39 (human clone CDM8-gp39 reduced). *CAS-457913-93-8*. INN. *Treatment of rheumatoid arthritis.* (Diosynth B.V.) ✧*Org 39141*

Ladostigil Tartrate [*2004*] (lad″ oh stij′ il). $2(C_{16}H_{20}N_2O_2)$. $C_4H_6O_6$. 694.80. [Ladostigil is INN.] (1) Carbamic acid, ethylmethyl-, (3*R*)-2,3-dihydro-3-(2-propynylamino)-1*H*-inden-5-yl ester, (2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1); (2) (3*R*)-3-(Prop-2-ynylamino)-2,3-dihydro-1*H*-inden-5-yl ethylmethylcarbamate (2*R*,3*R*)-tartarate (2:1). *CAS-209394-46-7; CAS-209394-27-4* [ladostigil]. *Treatment of Alzheimer's disease* (*an inhibitor of monoamine oxidase* (*MAO-A and B*)*, an acetylcholinesterase inhibitor, and a neuroprotectant*). (Teva, Israel) ✧*TV-3326*

† Brand name formerly used, and/or firm no longer concerned with this product.

Lanimostim [*2004*] (lan″ i moe′ stim). $C_{2146}H_{3346}N_{572}O_{686}S_{28}$. 49,033 daltons. (1) 4-221-Colony-stimulating factor 1 (human clone p3ACSF-69 reduced); (2) 4-221-Colony-stimulating factor 1 (human clone p3ACSF-69) (dimer). *CAS-117276-75-2*. INN. *Antineoplastic; anti-infective growth factor that acts on both progenitor and mature cells of the macrophage line.* (Eximias)

Lestaurtinib [*2004*] (le stor′ tin ib). $_{26}H_{21}N_3O_4$. 439.46. (1) 9,12-Epoxy-1*H*-diindolo[1,2,3-*fg*:3′,2′,1′-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one, 2,3,9,10,11,12-hexahydro-10-hydroxy-10-(hydroxymethyl)-9-methyl-, [9*S*-(9α,10β,12α)]-; (2) (9*S*,10*S*,12*R*)-10-Hydroxy-10-(hydroxymethyl)-9-methyl-2,3,9,10,11,12-hexahydro-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3′,2′,1′-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocin-1-one. *CAS-111358-88-4*. INN. *Treatment of tumors such as prostate and pancreatic carcinomas* (*selective inhibitor of tyrosine kinase*). (Cephalon) ✧*CEP-701; A-154475.0; SP924; KT5555*

Levotofisopam [*2004*] (lev″ oh toe fis′ oh pam). $C_{22}H_{26}N_2O_4$. 382.45. (1) 5*H*-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5*S*)-; (2) (–)-(5*S*)-1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine. *CAS-82059-51-6*. *Anxiolytic, autonomic instability.* (Cerilliant) ✧(*S*)-*tofisopam*

Lontucirev (Replicating Adenovirus) [*2004*] (lon too′ si rev). (1) DNA (human adenovirus ONYX-015); (2) E1B-55kDa gene-deleted adenovirus. *CAS-437981-77-6*. *Treatment of multiple cancers* (*E1-B deleted adenovirus; replication competent virus*). (Onyx) ✧*ONYX-015; CI-1042*

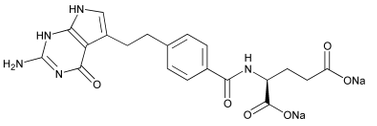
Mecasermin Rinfabate [*2004*] (mek a ser′ min). $C_{1231}H_{1967}N_{371}O_{384}S_{20}$. 36,304. (1) Insulin-like growth factor I (human), complex with insulin-like growth factor-binding protein IGFBP-3 (human); (2) Complex of recombinant human insulin-like growth factor I (somatomedin C) with recombinant human insulin-like growth factor-binding protein 3. *CAS-478166-15-3*. INN. *Antidiabetic.* Somatokine (Avecia, UK) ✧*rhIGF-I/rhIGFBP-3*

Paclitaxel Poliglumex [*2004*] (pak li tax′ el pol ee gloo′ mex). $(C_{52}H_{56}N_2O_{16})_n.(C_5H_7NO_3)_x$. (1) L-Glutamic acid, homopolymer, (1*R*,2*S*)-2-(benzoylamino)-1-[[[(2a*R*,4-*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl]oxy]carbonyl]-2-phenylethyl ester; (2) Poly(L-glutamic acid) partially γ-esterified with (1*R*,2*S*)-2-(benzoylamino)-1-[[[(2a*R*,4-*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-7,11-methano-1*H*-cyclodeca[3,4]benzo[1,2-*b*]oxet-9-yl]oxy]carbonyl]-2-phenylethyl. Molecular weight is approximately 45,000 daltons. *CAS-263351-82-2*. INN. *Anti-cancer therapy as a single agent or in combination with other anti-cancer therapies.* (Hauser CRO) ✧*CT-2103*

Panitumumab [*2004*] (pan i tue′ moo mab). $C_{6306}H_{9732}N_{1672}O_{1994}S_{46}$. 142,347. Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer. *CAS-339177-26-3*. INN. *Antineoplastic; treatment of EGF expressing tumors.* (Abgenix) ✧*ABX-EGF*

Pelitinib [*2004*] (pel i tye′ nib). $C_{24}H_{23}ClFN_5O_2$. 467.92. (1) 2-Butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-, (2*E*)-; (2) (2*E*)-*N*-[4-[(3-Chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide.*CAS-257933-82-7*. INN. *Treatment of cancer.* (Wyeth) ✧*EKB-569*

Pemetrexed Disodium [*2004*] (pem e trex′ ed). $C_{20}H_{19}N_5Na_2O_6$. 471.37. [Pemetrexed is INN and BAN.] (1) L-Glutamic acid, *N*-[4-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt; (2) Disodium *N*-[*p*-[2-(2-amino-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamate. *CAS-150399-23-8; CAS-137281-23-3* [pemetrexed]. *Antineoplastic* (*thymidylate synthase*). Alimta (Lilly) ✧*LY231514*



USP DI Category: Antineoplastic (specific thymidylate synthase inhibitor).

Perzinfotel [*2004*] (per zin foe′ tel). $C_9H_{13}N_2O_5P$. 260.20. (1) Phosphonic acid, [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]-; (2) [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid. *CAS-144912-63-0*. INN. *Treatment of neuropathic pain* (*NMDA receptor antagonist*). (Wyeth) ✧*EAA-090*

Prasugrel Hydrochloride [*2004*] (pra soo'pr grel). $C_{20}H_{20}FNO_3S.HCl$. 409.90. [Prasugrel is INN.] (1) Ethanone, 2-[2-(acetyloxy)-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl]-1-cyclopropyl-2-(2-fluorophenyl)-, hydrochloride; (2) 5-[(1*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride. *CAS-389574-19-0; CAS-150322-43-3* [prasugrel]. *Inhibits platelet aggregation* (*platelet ADPP 2Y12 antagonist*). (Lilly) ✧*LY640315*

Regadenoson [*2004*] (re ga den′ oh son). $C_{15}H_{18}N_8O_5$. 390.35. (1) Adenosine, 2-[4-[(methylamino)carbonyl]-1*H*-pyrazol-1-yl]-; (2) 1-(6-Amino-9-β-D-ribofuranosyl-9*H*-purin-2-yl)-*N*-methyl-1*H*-pyrazole-4-carboxamide. *CAS-313348-27-5*. INN. *Coronary vasodilator for intravenous use as an adjunct, or pharmacologic stress agent, in radionuclide myocardial perfusion imaging in patients unable to exercise adequately* (A_{2A} *adenosine receptor agonist*). (Tetrionics) ✧*CVT-3146*

Retapamulin [*2004*] (re tap′′ a mue′ lin). $C_{30}H_{47}NO_4S$. 517.80. (1) Acetic acid, [[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]thio]-, (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester; (2) (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyl-5-hydroxy-4,6,9,10-tetramethyl-1-oxodecahydro-3a,9-propano-3a*H*-cyclopenta[8]annulen-8-yl [[(1*R*,3*s*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]sulfanyl]acetate. *CAS-224452-66-8*. INN. *Topical antibiotic for secondarily infected traumatic lesions* (*SITL*) *and secondarily infected dermatoses* (*SID*) *or impetigo.* (GlaxoSmithKline) ✧*SB-275833*

Secretin [*2004*] (see′ kret in). $C_{130}H_{220}N_{44}O_{40}$ (human) . 3039.40 (human); $C_{130}H_{220}N_{44}O_{41}$ (porcine). 3055.50 (porcine). CHEMICAL NAMES (human): (1) Secretin (porcine), 15-L-glutamic acid-16-glycine-; (2) L-Histidyl-L-seryl-L-α-aspartylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-glutamyl-L-leucyl-L-seryl-L-arginyl-L-leucyl-L-arginyl-L-α-glutamylglycyl-L-alanyl-L-arginyl-L-leucyl-L-glutaminyl-L-arginyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide. CHEMICAL NAMES (porcine): (1) Secretin (porcine): (2) L-Histidyl-L-seryl-L-α-aspartylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-glutamyl-L-leucyl-L-seryl-L-arginyl-L-leucyl-L-arginyl-L-α-aspartyl-L-seryl-L-alanyl-L-arginyl-L-leucyl-L-glutaminyl-L-arginyl-L-leucyl-L-leucyl-L-glutaminylglycyl-L-leucyl-L-valinamide. *CAS-108153-74-8* [human]; *CAS-17034-35-4* [porcine]; *CAS-1393-25-5*. INN; BAN; JAN; DCF; MI. *Stimulates pancreatic and gastric secretions to aid in the diagnosis of pancreatic exocrine dysfunction and the diagnosis of gastrinoma.* (Chesapeake); (PolyPeptide); Secretin-Kabi (KabiVitrum, Sweden) *[NOTE—The source of the product* (*human, porcine, etc.*) *must be indicated in the labeling.]*

Selodenoson [*2004*] (sel oh den′ oh son). $C_{17}H_{24}N_6O_4$. 376.41. (1) β-D-Ribofuranuronamide, 1-[6-(cyclopentylamino)-9*H*-purin-9-yl]-1-deoxy-*N*-ethyl-; (2) 1-[6-(Cyclopentylamino)-9*H*-purin-9-yl]-1-deoxy-*N*-ethyl-β-D-ribofuranuronamide. *CAS-110299-05-3*. INN. *Management of atrial fibrillation and atrial flutter.* (Torcan) ✧*DTI-0009*

Sugammadex Sodium [*2004*] (soo gam′ ma dex). $C_{72}H_{104}Na_8O_{48}S_8$. 2178. (1) γ-Cyclodextrin, 6A,6B,6C,6D,6E,7F,6G,6H-octakis-*S*-(2-carboxyethyl)-6A,6B,6C,6D,6E,7F,6G,6H-octathio-, octasodium salt; (2) Octasodium 6,6′,6′′,6′′′,6′′′′,6′′′′′,6′′′′′′,6′′′′′′′-octakis-*S*-(2-carboxylatoethyl)-6,6′,6′′,6′′′,6′′′′,6′′′′′,6′′′′′′,6′′′′′′′-octathiocyclo-α-(1→4)-D-octaglucopyranoside. *CAS-343306-79-6*. *Reversal agent for neuromuscular blocking agents.* (N.V. Organon, Netherlands) ✧*Org 25969*

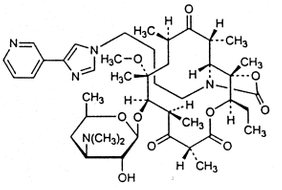
Taltobulin [*2004*] (tal toe bue′ lin). $C_{27}H_{43}N_3O_4$. 473.65. (1) L-Valinamide, *N*,β,β-trimethyl-L-phenylalanine-*N*-[(1*S*,2*E*)-3-carboxy-1-(1-methylethyl)-2-butenyl]-*N*,3-dimethyl-; (2) (4*S*)-4-[[(2*S*)-3,3-Dimethyl-2-[[(2*S*)-3-methyl-2-(methylamino)-3-phenylbutanoyl]amino]butanoyl]methylamino]-2,5-dimethylhex-2-enoic acid. *CAS-228266-40-8*. INN. *Treatment of solid tumors.* (Wyeth) ✧*HTI-286*

Tandutinib [*2004*] (tan doo tye′ nib). $C_{31}H_{42}N_6O_4$. 562.70. (1) 1-Piperazinecarboxamide, 4-[6-methoxy-7-[3-(1-piperidinyl)-propoxy]-4-quinazolinyl]-*N*-[4-(1-methylethoxy)phenyl]-; (2) 4-[6-Methoxy-7-[3-(piperidin-1-yl)propoxy]quinazolin-4-yl]-*N*-[4-(1-methylethoxy)phenyl]piperazine-1-carboxamide. *CAS-387867-13-2*. INN. *Treatment of cardiovascular diseases, fibrotic diseases and acute myelogenous leukemia* (*tyrosine kinase inhibitor*). (Regis) ✧*CT 53518*

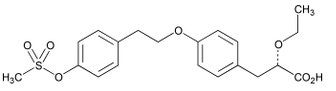
Telavancin Hydrochloride [*2004*] (tel a vam′ sin). $C_{80}H_{106}Cl_2N_{11}O_{27}P.HCl$. 1792.10. [Telavancin is INN.] (1) Vancomycin, $N^{3''}$-[2-(decylamino)ethyl]-29-[[(phosphonomethyl)amino]methyl]-, monohydrochloride; (2) (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-3-(2-Amino-2-oxoethyl)-10,19-dichloro-44-[[2-*O*-[3-[[2-(decylamino)ethyl]amino]-3-*C*-methyl-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl]-β-D-glucopyranosyl]oxy]-7,22,28,30,32-pentahydroxy-6-[[(2*R*)-4-methyl-2-(methylamino)pentanoyl]amino]-2,5,24,38,39-pentaoxo-29-[[(phosphonomethyl)amino]methyl]-

2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-8,11:18,21-dietheno-23,36-(iminomethano)-22*H*-13,16:31,35-dimetheno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid monohydrochloride. *CAS-560130-42-9; CAS-372151-71-8* [telavancin]. *Antibacterial agent active against gram-positive pathogens.* (Theravance) ✧*Td-6424*

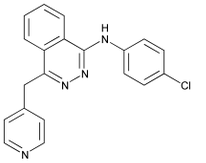
Telithromycin [*2004*] (tel ith″ roe mye′ sin). $C_{43}H_{65}N_5O_{10}$. 812.00. (1) Erythromycin, 3-de[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1*H*-imidazol-1-yl]butyl]imino]-; (2) (3a*S*,4*R*,7*R*,9*R*,10*R*,11*R*,13*R*,15*R*,15a*R*)-4-Ethyl-11-methoxy-3a,7,9,11,13,15-hexamethyl-1-[4-[4-(pyridin-3-yl)-1*H*-imidazol-1-yl]butyl]-10-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]octahydro-2*H*-oxacyclotetradecino[4,3-*d*]oxazole-2,6,8,14(1*H*,7*H*,9*H*)-tetrone. *CAS-191114-48-4; CAS-173838-31-8*. INN; BAN. *Antimicrobial* (*via inhibition of bacterial protein synthesis*). Ketek (Aventis) ✧*HMR 3647*



Tesaglitazar [*2004*] (tes″ a gli′ ta zar). $C_{20}H_{24}O_7S$. 408.47. (1) Benzenepropanoic acid, α-ethoxy-4-[2-[4-[(methylsulfonyl)oxy]phenyl]ethoxy]-, (α*S*)-; (2) (2*S*)-2-Ethoxy-3-[4-[2-[4-[(methylsulfonyl)oxy]phenyl]ethoxy]phenyl]propanoic acid. *CAS-251565-85-2*. INN. *Treatment of type 2 diabetes and insulin resistance syndrome.* Galida (AstraZeneca) ✧*AR-H039242XX*



Vatalanib [*2004*] (va tal′ an ib). $C_{20}H_{15}ClN_4$. 346.81. (1) 1-Phtalazinamine, *N*-(4-chlorophenyl)-4-(4-pyridinylmethyl)-; (2) *N*-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phtalazin-1-amine.*CAS-212141-54-3*. INN. *Treatment of tumors.* (Novartis Pharma) ✧*PTK787*



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 68 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 18, No. 2, 2004.

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
Abatacept	*Immunomodulator*
Acotiamide	*Antiemetic (parasympathomimetic)*
Alagebrium Chloride	*Agent influencing protein glycosylation*
Alglucosidase Alfa	*Enzyme*
Armodafinil	*Psychostimulant*
Bamirastine	*Histamine H_1 receptor antagonist*
Befetupitant	*Neurokinin NK_1 receptor antagonist*
Belotecan	*Antineoplastic agent*
Carmoterol	*Bronchodilator*
Cetilistat	*Gastro-intestinal lipase inhibitor*
Dasantafil	*Vasodilator*
Daxalipram	*Phosphodiesterase IV inhibitor*
Denufosol	*P2Y2 receptor agonist*
Depelestat	*Neutrophil elastase inhibitor*
Dirlotapide	*Antihyperlipidemic (veterinary drug)*
Edaglitazone	*Antidiabetic agent*
Exbivirumab	*Antiviral*
Fampronil	*Antiparasitic agent (veterinary drug)*
Fidexaban	*Blood coagulation factor Xa inhibitor*
Fingolimod	*Immunomodulator*
Gadodenterate	*MNR contrast agent*
Gantacurium Chloride	*Neuromuscular blocking agent*
Golimumab	*Immunomodulator*
Idronoxil	*Antineoplastic agent*
Imiglitazar	*Antidiabetic agent*
Indacaterol	*Bronchodilator*
Indibulin	*Antineoplastic agent*
Ismomultin Alfa	*Antirheumatic*
Lanimostim	*Immunomodulator*
Lemuteporfin	*Photosensitizing agent*
Lenalidomide	*Antineoplastic agent*
Lestaurtinib	*Antineoplastic agent*
Libivirumab	*Antiviral*
Maraviroc	*Antiviral*
Mecasermin Rinfabate	*Antidiabetic agent*
Milataxel	*Antineoplastic agent*
Mirococept	*Anti-inflammatory*
Paclitaxel Ceribate	*Antineoplastic agent*
Palosuran	*Urotensin receptor antagonist*
Panitumumab	*Antineoplastic agent*
Pegamotecan	*Antineoplastic agent*
Pelitinib	*Antineoplastic agent*
Perflubutane	*Ultrasound contrast agent*
Perzinfotel	*NMDA receptor antagonist*
Prasugrel	*Platelet aggregation inhibitor*
Radafaxine	*Antidepressant*
Ranirestat	*Aldose reductase inhibitor*
Regadenoson	*Adenosine receptor A agonist*
Reparixin	*Anti-inflammatory action through the inhibition of cytokine (IL-8)*
Retapamulin	*Antibiotic*
Revaprazan	*Acid pump inhibitor*
Rilpivirine	*Antiviral*
Ritobegron	*Beta$_3$-adrenoreceptor agonist*
Robenacoxib	*Selective cyclo-oxygenase inhibitor (veterinary drug)*
Rostafuroxin	*Hypotensive agent*
Selodenoson	*Selective adenosine A_1 receptor agonist*
Taltobulin	*Antineoplastic agent*
Tandutinib	*Antineoplastic agent*
Teglicar	*Palmitoylcarnitine transferase I inhibitor*
Telavancin	*Antibiotic*
Tetomilast	*Phosphodiesterase IV inhibitor*
Tifuvirtide	*Antiviral*
Topilutamide	*Antiandrogen*
Torapsel	*Antithrombotic agent*
Trodusquemine	*Appetite suppressant*
Vandetanib	*Angiogenesis inhibitor*
Vestipitant	*Neurokinin NK_1 receptor antagonist*
Yttrium (^{90}Y) Tacatuzumab	*Antineoplastic agent*

Recommended International Nonproprietary Names

The following 58 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 18, No. 1, 2004.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Adargileukin Alfa	Edotecarin	Icofungipen	Pritumumab
Alamifovir	Edratide	Icrocaptide	Ralfimamide
Aprinocarsen	Elsilimomab	Iferanserin	Rebimastat
Belimumab	Elvucitabine	Istradefylline	Segestrone
Cantuzumab Mertansine	Epitumomab Cituxetan	Ixabepilone	Semapimod
Cimicoxib	Eptotermin Alfa	Ladostigil	Sufugolix
Dabuzalgron	Exatecan Alideximer	Lapatinib	Tacapenem
Dacinostat	Exenatide	Lomeguatrib	Tafluprost
Dalbavancin	Firocoxib	Odiparcil	Talizumab
Deligoparin Sodium	Fispemifene	Omiganan	Technetium (99mTc) Nitridocade
Desvenlafaxine	Fluorescein Lisicol	Pactimibe	Tesofensine
Dibotermin Alfa	Freselestat	Patupilone	Tifenazoxide
Diquafosol	Galiximab	Pertuzumab	Tisocalcitate
Disermolide	Hemoglobin Raffimer	Pixantrone	Ulifloxacin
Edifoligide			Varenicline

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
Acallantide Ecallantide Epicallantide Epicallide Epicallintide Epikallintide Pacallantide	*Treatment of hereditary angioedema cardiopulmonary bypass (plasma kallikrein inhibitor)*
Adarolimus Etosirolimus Tetrazolimus Tetrolimus Tetrosirolimus Tezolimus Tezorolimus Zolimus	*Antifungal macrolide (drug component of an investigational phosphoryl choline polymer-coated eluting stent, currently under evaluation for the prevention of coronary restenosis following stent replacement*
Afatacib Afenatacib Afenatastat Apratastat Fanatacib Fapenatacib Fapenetacib Pratacib Rafatacib Rafenatacib Rafutastat Tratacib	*Treatment of rheumatoid arthritis*
Afboximab Afociximab Afotuximab Boxatuximab Valiximab Volociximab Volotuximab	*Anti-angiogenic agent to treat solid tumors and age-related macular degeneration*
Agipartrant Sulfate Torapiparant Sulfate Vogrelapar Sulfate Voparagrel Sulfate Voparonant Sulfate Voraparpiant Sulfate	*Treatment of thrombosis (orally active protease-activated receptor (PAR)1 antagonist)*
Agotinib Aneoganib Axisanib Axitinib Trexisanib Trexitinib	*Treatment of cancer*

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

Suggested USAN	Category
Agvexital	*Anti-imflammatory and antimicrobial*
Argenantal	
Argentunantal	
Argevexital	
Nanocrystalline Silver	
Silvenantal	
Silver Nanocrystalline	
Silver Nanotalline	
Silvervexital	
Silvexital	
Aliskiren	*Treatment of hypertension*
Amyglybril	*Treatment of mild-to-moderate Alzheimer's disease, treatment of cerebral amyloid angiopathy (antiamyloidotic)*
Amytargam	
Betamilod	
Prevamilod	
Preveglybril	
Prevetargam	
Talamibril Disodium	
Zeprotargam	
Zontargam	
Amyglybril	*Treatment of Secondary (AA) Amyloidosis*
Amytargam	
Fibramilod	
Fibritargam	
Prevamibril Disodium	
Prevamilod	
Preveglybril	
Zontargam	
Apaxaban	*Anticoagulant; Antithrombotic*
Aprixaban	
Belaxaban	
Cinaxaban	
Apilimumab	*Treatment of oncology disease and HIV infection*
Balimumab	
Ipilimumab	
Oblimimumab	
Palimumab	
Peclimumab	
Aptumumab	*Treatment of cancer*
Lontumumab	
Mapatumumab	
Tractumumab	
Aquifocon A	*Hydrophobic contact lens material*
Aquilafocon A	
Aquilfocon A	
Aquilofocon A	
Atebineuzumab	*Treatment of Alzheimer's disease*
Bapineuzumab	
Bapneuzumab	
Pasineuzumab	
Atratinib Malate	*Treatment of cancer*
Senitinib Malate	
Sunaritinib Malate	
Sunitinib Malate	
Susitinib Malate	

Suggested USAN	Category
Avaracetam	*Treatment of epilepsy, neuropathic pain and essential tremor*
Axiaracetam	
Axivaracetam	
Bravaracetam	
Brivaracetam	
Ziaracetam	
Becorotan Hydrochloride	*Treatment of Alzheimer's disease (5-HT1a agonist)*
Becorotane Hydrochloride	
Lecorotan Hydrochloride	
Lecorotane Hydrochloride	
Lecozotan Hydrochloride	
Lecozotane Hydrochloride	
Belatacept	*Prevention of allograft rejection in recipients of solid organ transplants; prevention of graft-versus-host disease following bone marrow transplantation; treatment of autoimmune diseases and conditions such as rheumatoid arthritis and Type 1 diabetes*
Elatacept	
Leatacept	
Belizumab	*Treatment of rheumatoid arthritis*
Crelizumab	
Lolizumab	
Relizumab	
Ubelizumab	
Belocitabine	*Treatment of HIV-1 and HIV-2 infection*
Dexelvucitabine	
Dexvucitabine	
Revacitabine	
Revcitavir	
Revucitabine	
Tesacitabine	
Tesrevir	
Belotecan Hydrochloride	*Antineoplastic, used in the treatment of advanced solid tumor malignancies refractory to standard therapies*
Bevafermin	*Treatment and/or prevention of mucositis*
Brevafermin	
Tegafermin	
Tepafermin	
Velafermin	
Cardoxinyl Hydrochloride	*Treatment of patients with atrial fibrillation and atrial flutter*
Hexodinyl Hydrochloride	
Mefenexane Hydrochloride	
Cenicline Galactarate	*Treatment of ulcerative colitis*
Rivanicline Galactarate	
Rivinicline Galactarate	
Rovanicline Galactarate	
Cilansetron	*Treatment of diarrhea-predominant Irritable Bowel Syndrome*
Cilansetron Hydrochloride	*Treatment of diarrhea-predominant Irritable Bowel Syndrome*

Suggested USAN	Category
Cixicirfor Ericixafor Ericixcrant Ericixirfor Plericixafor Plerixafor	*Stem cell mobilization (CXCR4 antagonist)*
Darifenacin	*Treatment of overactive bladder*
Darunavir	*Treatment of HIV infection*
Delamostat Golamostat Relamostat Zelamostat	*Treatment of osteoporosis*
Desancycline Incemocline Incyclinor Incymastat Incyplemib Intepacib Inteplemib Maztecinor	*Treatment of rosacea; treatment of acute respiratory distress syndrome (ARDs) (chemically modified tetracycline [CMT] which is claimed to inhibit multiple proteases and cytokines)*
Diaplastinin Diaplaxtinin	*Treatment of fibrinolytic impairment disease*
Doripenem	*Antibiotic*
Edotecarin	*Antineoplastic (topoisomerase I inhibitor)*
Emulsebinex Prosepibex Sepebinex	*Treatment of patients with suspected or confirmed gram-negative severe sepsis with the intent of reducing 28-day all-cause mortality*
Etravirine	*Treatment of HIV infection*
Evandiracetam Seletracetam Vantiracetam	*Treatment of epilepsy, neuropathic pain, and essential tremor*
Fesoterodine Hydrogen Fumarate	*Treatment of overactive bladder with symptoms of urinary urgency, frequency and/or urge incontinence*
Forodesine	*Treament of T-cell malignancies such as acute lymphoblastic leukemia (ALL) and cutaneous T-cell lymphoma (CTCL)*
Fulvotaxel Misotaxel Naltotaxel	*Treatment of breast cancer*
Glutatrexed Ammonium Gretopterin Ammonium Loropterin Ammonium Oropterin Ammonium Orotrexed Ammonium Talopterin Ammonium	*Antineoplastic*
Hulaplexumid Immunoplexumid Lexlimogene (HLA-B7 Plasmid) Plasmid-huHLA B7 Ulaplastumogene Ulaplasumogene (HLA B7)	*Treatment of melanoma (HLA B7) antigen expression via DNA transfection*
Intadotin Hydrochloride Sintadotin Hydrochloride Synthadotin Hydrochloride Tasidotin Hydrochloride	*Treatment of patients with advanced refractory neoplasms*
Iodine Acrylex Iodine Polacryterlex Iodine Poteracrylex Iodine Povacrylex	*Topical antiseptic*
Ipronicline Ispronicline Promenicline Sarenicline Tivonicline	*Treatment of cognitive and memory disorders (nicotine receptor partial agonist)*
Manalopan Bromide Menaltrexium Bromide Menaltrexone Bromide Methylnaltrexone Bromide Metilnaltrexium Bromide Metilnaltrexone Bromide Metrexopan Bromide Nalpromium Bromide Nalquatrone Bromide Oprinone Bromide	*Treatment of peripheral side effects of opoid therapy (peripheral opoid receptor antagonist)*
Mitratapide	*Management of obesity in dogs*
Nolovizumab Numavizumab Ralivizumab Reslivizumab Resyvizumab Umavizumab	*Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk*
Olanzapine Pamoate	*Treatment of schizophrenia (selective monoaminergic antagonist)*
Pagibaximab Pediabacximab Pilabaximab Podobaximab	*Prevention of staphylococcal sepsis in premature infants*
Perflubutane Perflutan Perflutane	*A third-generation ultrasound contrast agent intended for assessing myocardial perfusion (blood flow within the heart muscle) in patients with coronary artery disease*
Resatumumab Restumumab Rosutumumab Tiratumumab Tritumumab	*Treatment of oncologic diseases; treatment of relapsed or refractory CD30 positive lymphoma including Hodgkin's disease*
Rimonabant	*Smoking cessation and anti-obesity*

Nomenclature

Suggested USAN	Category
Selanzymin	*Anti-inflammatory and antimicrobial*
Selezymin	
Selmimase	
Selmimetase	
Somimase	
Somimetase	
Sopasemim Manganese	
Sumimetase	
Suprozymin	
Zormimase	
Tisocalcitate	*Topical treatment of plaque-type psoriasis*
Valepcitabine Dihydrochloride	*Treatment of chronic hepatitis C (HCV RNA polymerase inhibitor)*
Valeprucitabine Dihydrochloride	
Valopcitabine Dihydrochloride	
Valopicitabine Dihydrochloride	
Valpercitabine Dihydrochloride	
Zanolimumab	*Treatment of rheumatoid arthritis (RA), psoriasis (PSO), and cutaneous T-cell lymphoma (CTCL)*

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.

Suggested INN	Category
Acallantide Ecallantide Epicallantide Pacallantide	*Treatment of hereditary angioedema; cardiopulmonary bypass (plasma kallikrein inhibitor)*
Actavirine Etravirine Tetraviridine Vidavirine Vitravirine	*Treatment of HIV infection*
Actinovir Arunavir Darunavir Difanavir	*Treatment of HIV infection*
Adarolimus Tezorolimus	*Antifungal macrolide (drug component of an investigational phosphoryl choline polymer-coated eluting stent, currently under evaluation for the prevention of coronary restenosis following stent replacement)*
Aliskiren	*Antihypertensive*
Apaxaban Aprixaban	*Anticoagulant; antithrombotic*
Apilimumab Ipilimumab Oblimimumab	*Treatment of oncological diseases and HIV infection*
Apratastat Pratacib	*Treatment of rheumatoid arthritis*
Arbuprodene Aviprodene Keniprodene Palprodene	*Neurotrophic and neuroprotective compound expected to be used in the prevention of neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases)*
Avanabant Loranabant Surinabant	*Treament of obesity/metabolic disorders and smoking cessation*
Avaracetam Bravaracetam Brivaracetam	*Treatment of epilepsy, neuropathic pain and essential tremor*
Bapineuzumab	*Treatment of Alzheimer's disease*
Belatacept	*Prevention of allograft rejection in recipients of solid organ transplants; prevention of graft-versus-host disease following bone marrow transplantation; treatment of autoimmune diseases and conditions (selective co-stimulation modulator which binds to the B7 family of molecules expressed in antigen-presenting cells)*
Belotecan Pamitecan Travitecan	*Antineoplastic, used in the treatment of advanced solid tumor malignancies refractory to standard therapies*
Calcimetriol Isocalcitol Isocalcitriol Procalcitol Tisocalcitate	*Topical treatment of plaque-type psoriasis*
Celiarone Isoparone Monarone	*Antiarrhythmic related to amiodarone*
Cilansetron	*Treatment of diarrhea-predominant Irritable Bowel Syndrome*
Crelizumab	*Treatment of rheumatoid arthritis*

Suggested INN	Category
Cyclorelin Follirelin Ovorelin	*Endogenous substance regulating secondary hormonal processes in the body via the central nervous system*
Danlimumab Dralimumab Genlimumab Zanolimumab	*Treatment of rheumatoid arthritis (RA), psoriasis (PSO), and Cutaneous T-cell Lymphoma (CTCL)*
Darifenacin Dasifenacin	*Treatment of overactive bladder*
Dianaicline Efinicline Livanicline Solinicline	*Aid to smoking cessation and maintenance of abstinence from smoking*
Diaplastinin Diaplaxtinin	*Treatment of fibrinolytic impairment disease*
Dipromine Fesoterodine Isofurine Mesofidine	*Treatment of incontinence*
Dirlotapide Mifratapide	*Management of obesity in dogs*
Doripenem Toripenem	*Antibiotic*
Edocarban Edocarbax Edotecarin Incarbax	*Antineoplastic (topoisomerase I inhibitor)*
Forodesine	*Treatment of T-cell malignancies such as acute lymphoblastic leukemia (ALL) and cutaneous T-cell lymphoma (CTCL)*
Impronakib Kordkanact Motokanarin	*Treament of spinal cord injury (K^+ channel blocker plus voltage dependent Na^+ channel blocker)*
Ipronicline Ispronicline Tivonicline	*Treatment of cognitive and memory disorders (nicotine receptor agonist)*
Lecozotan	*Treatment of Alzheimer's disease (5-HT1a agonist)*
Legametasone Renametasone Runometasone	*Intranasal and inhaled steroid to reduce swelling and inflammation to relieve common nasal symptoms (when used as an intranasal steroid) or to suppress inflammation within airways (when used as an inhaled steroid to asthma)*
Lexlimogene (HLA-B7 Plasmid)	*Treatment of melanoma (HLA B7) antigen expression via DNA transfection*
Mapatumumab	*Treatment of cancer*
Olanzapine Pamoate	*Treatment of schizophrenia (selective monoaminergic antagonist)*
Pagibaximab	*Prevention of staphylococcal sepis in premature infants*
Perflisoban Perflisotan Perfluban Perflubutane Perfluroban Perflutan	*A third-generation ultrasound contrast agent intended for assessing myocardial perfusion (blood flow within the heart muscle) in patients with coronary artery disease*
Plericixafor Plerixafor	*Stem cell mobilization (CXCR4 antagonist)*
Prevamibril Disodium	*Treament of secondary (AA) amiloidosis*
Rimonabant	*Smoking cessation and anti-obesity*
Rivanicline Galactarate Rovanicline Galactarate	*Treatment of ulcerative colitis*
Seletracetam	*Treatment of epilepsy, neuropathic pain, and essential tremor*
Senitinib Sunitinib	*Treatment of cancer*
Sopasemim Manganese	*Treatment of pain and inflammation (superoxide dismutase mimetic)*
Talamibril Disodium	*Treatment of mild to moderate Alzheimer's disease; treatment of cerebral amyloid angiopathy (antiamyloidotic)*
Talopterin Ammonium	*Antineoplastic*
Tasidotin	*Treatment of advanced, refractory neoplasms*
Valopicitabine	*Treatment of chronic hepatitis C (HCV RNA polymerase inhibitor)*
Volociximab	*Anti-angiogenic agent to treat solid tumors and age-related macular degeneration*

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[*Note—This index covers Vol. 31 No. 1, pp. 1–288*]

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USP CATALOG

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
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	$162
1012768	Alcohol (1.2 mL/ampule; 5 ampules)	F0D030	$162
1012772	Dehydrated Alcohol (1.2 mL/ampule; 5 ampules)	F0D031	$162
1012699	Alcohol Determination–Acetonitrile (5 mL/ampule; 5 ampules)	F0C419	$162
1012688	Alcohol Determination–Alcohol (5 mL/ampule; 5 ampules)	F0C399	$162
1027302	Amiodarone Hydrochloride (200 mg)	F0D257	$162
1029501	Amlodipine Besylate (200 mg)	F0D167	$162
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	$162
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	$162
1048641	Benazepril Related Compound C (50 mg)	F0C425	$506
1071439	Positive Bioreaction (3 strips; 10 cm x 1 cm)	F0D014	$338
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086	$541
1076341	Boric Acid (1 g) (AS)	F0D036	$208
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	$162
1086334	Calcium Acetate (1 g) (AS)	F0D156	$162
1086403	Calcium Carbonate (1 g) (AS)	F0D099	$162
1086436	Calcium Chloride (1 g) (AS)	F0D153	$162
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	$162
1087359	Calcium Stearate (2 g) (AS)	F0D255	$162
1087406	Calcium Sulfate (1 g) (AS)	F0D236	$162
1087701	Candelilla Wax (250 mg)	F0D123	$162
1091505	Caprylocaproyl Polyoxylglycerides (200 mg)	F0C312	$182
1098027	Cefpodoxime Proxetil (350 mg)	F0C192	$162
1098322	Cellaburate (350 mg) (Cellulose Acetate Butyrate)	F0D220	$162
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406	$541
1111307	Chlorhexidine Related Compounds (50 mg)	F0D017	$506
1115545	Chlorogenic Acid (50 mg)	F0C420	$162
1140429	Clonidine Related Compound B (25 mg)	F0C403	$506
1148806	Corn Oil (1 g) (AS)	F0D181	$162
1150207	Cottonseed Oil (1 g) (AS)	F0D173	$162
1179650	Dextran T-10 (200 mg)	F0D238	$162
1187080	Dibutyl Phthalate (200 mg)	F0D125	$162
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	$162
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018	$541
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019	$541
1269414	Fenbendazole Related Compound A (30 mg)	F0D009	$506
1269425	Fenbendazole Related Compound B (30 mg)	F0D008	$506
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	$162
1270377	Fexofenadine Hydrochloride (200 mg)	F0D244	$162
1270388	Fexofenadine Related Compound A (25 mg)	F0D245	$506
1270399	Fexofenadine Related Compound B (25 mg)	F0D246	$506
1271700	Fluconazole (200 mg)	F0D262	$162
1271711	Fluconazole Related Compound A (10 mg)	F0D080	$506
1271722	Fluconazole Related Compound B (10 mg)	F0D081	$506
1288463	Gemcitabine Hydrochloride (200 mg)	F0D037	$162
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	$562
1311306	Homopolymer Polypropylene (3 Strips)	F0C096	$162
1335279	Hypromellose Acetate Succinate (100 mg)	F0D275	$162
1356698	Lactase (200 mg)	F0D032	$162
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	$162
1356847	Lamivudine Resolution Mixture A (10 mg)	F0D024	$506
1356950	Lauroyl Polyoxylglycerides (500 mg) (AS)	F0D020	$162
1358503	Leuprolide Acetate (200 mg)	F0C430	$1,586
1367708	Linoleoyl Polyoxylglycerides (100 mg)	F0C283	$162
1370280	Loratadine Related Compound A (15 mg)	F0D229	$506
1370291	Loratadine Related Compound B (15 mg)	F0D230	$506
1370462	Losartan Potassium (250 mg)	F0D287	$162
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	$162
1374248	Magnesium Chloride (1 g) (AS)	F0D157	$162
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	$162
1374340	Magnesium Stearate (5 g) (AS)	F0D214	$162
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	$162
1375069	Mangafodipir Trisodium (200 mg)	F0D272	$162
1375070	Mangafodipir Related Compound A (15 mg)	F0D266	$506
1375080	Mangafodipir Related Compound B (15 mg)	F0D267	$506
1375127	Manganese Chloride (1 g) (AS)	F0D150	$162
1375149	Manganese Sulfate (1 g) (AS)	F0D151	$162
1378012	Medroxyprogesterone Acetate Related Compound A (25 mg)	F0C427	$520
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	$582
1441298	Metoprolol Succinate (200 mg)	F0C415	$162
1444279	Mirtazapine (350 mg)	F0D155	$832
1445211	Mitoxantrone System Suitability Mixture (0.3 mg)	F0D010	$520

New Items at a Glance (*Continued*)

Cat. No.	Description	Curr. Lot	Price
1449530	Nabumetone Related Compound A (15 mg)	F0D165	$506
1457469	Naratriptan Hydrochloride (125 mg)	F0C360	$216
1460703	Nevirapine Anhydrous (100 mg)	F0D159	$162
1460714	Nevirapine Hemihydrate (100 mg)	F0D034	$162
1460725	Nevirapine Related Compound A (15 mg)	F0D035	$506
1460736	Nevirapine Related Compound B (15 mg)	F0D033	$506
1478152	Oleoyl Polyoxylglycerides (100 mg)	F0C313	$162
1478254	Olive Oil (1 g) (AS)	F0D175	$162
1478630	Ondansetron Resolution Mixture (50 mg)	F0D242	$506
1485125	Oxybutynin Related Compound B (20 mg)	F0D061	$506
1485136	Oxybutynin Related Compound C (20 mg)	F0D062	$506
1492040	Palm Oil (1 g) (AS)	F0D179	$162
1500262	Paroxetine Related Compound E Mixture (25 mg)	F0D225	$506
1500273	Paroxetine Related Compound F (10 mg)	F0D237	$506
1500284	Paroxetine Related Compound G (10 mg)	F0D110	$506
1500557	Peanut Oil (1 g) (AS)	F0D171	$162
1525707	Phenothiazine (500 mg) (AS)	F0D231	$162
1526200	Phenoxyethanol (500 mg)	F0D069	$162
1547925	Polysorbate 20 (2 g) (AS)	F0D130	$162
1547936	Polysorbate 40 (2 g) (AS)	F0D204	$162
1547947	Polysorbate 60 (2 g) (AS)	F0D131	$162
1547969	Polysorbate 80 (2 g) (AS)	F0D132	$162
1548101	Potassium Benzoate (1 g) (AS)	F0D161	$162
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	$162
1548167	Potassium Carbonate (1 g) (AS)	F0D075	$162
1548190	Potassium Chloride (1 g) (AS)	F0D127	$162
1548280	Potassium Iodide (1 g) (AS)	F0D078	$162
1548407	Potassium Sorbate (1 g) (AS)	F0D264	$162
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	$162
1601102	Residual Solvents Mixture - Class 1 (1.2 mL/ampule; 3 ampules)	F0C407	$162
1601146	Residual Solvent Class 1 - Benzene (1.2 mL/ampule; 3 ampules)	F0C408	$162
1601168	Residual Solvent Class 1 - Carbon Tetrachloride (1.2 mL/ampule; 3 ampules)	F0C409	$162
1601180	Residual Solvent Class 1 - 1,2-Dichloroethane (1.2 mL/ampule; 3 ampules)	F0C412	$162
1601204	Residual Solvent Class 1 - 1,1-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0C411	$162
1601226	Residual Solvent Class 1 - 1,1,1-Trichloroethane (1.2 mL/ampule; 3 ampules)	F0C410	$162
1601281	Residual Solvents Class 2 - Mixture A (1.2 mL/ampule; 3 ampules)	F0D051	$162
1601306	Residual Solvent Class 2 - Mixture C (1.2 mL/ampule; 3 ampules)	F0D182	$162
1601340	Residual Solvent Class 2 - Acetonitrile (1.2 mL/ampule; 3 ampules)	F0D049	$162
1601361	Residual Solvent Class 2 - Chlorobenzene (1.2 mL/ampule; 3 ampules)	F0D048	$162
1601383	Residual Solvent Class 2 - Chloroform (1.2 mL/ampule; 3 ampules)	F0D186	$162
1601408	Residual Solvent Class 2 - Cyclohexane (1.2 mL/ampule; 3 ampules)	F0D047	$162
1601420	Residual Solvent Class 2 - 1,2-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0D040	$162
1601463	Residual Solvent Class 2 - 1,2-Dimethoxyethane (1.2 mL/ampule; 3 ampules)	F0D185	$162
1601485	Residual Solvent Class 2 - N,N-Dimethylacetamide (1.2 mL/ampule; 3 ampules)	F0D169	$162
1601500	Residual Solvent Class 2 - N,N-Dimethylformamide (1.2 mL/ampule; 3 ampules)	F0D189	$162
1601521	Residual Solvent Class 2 - 1,4-Dioxane (1.2 mL/ampule; 3 ampules)	F0D050	$162
1601543	Residual Solvent Class 2 - 2-Ethoxyethanol (1.2 mL/ampule; 3 ampules)	F0D195	$162
1601565	Residual Solvent Class 2 - Ethylene Glycol (1.2 mL/ampule; 3 ampules)	F0D191	$162
1601587	Residual Solvent Class 2 - Formamide (1.2 mL/ampule; 3 ampules)	F0D188	$162
1601623	Residual Solvent Class 2 - Methanol (1.2 mL/ampule; 3 ampules)	F0D045	$162
1601645	Residual Solvent Class 2 - 2-Methoxyethanol (1.2 mL/ampule; 3 ampules)	F0D194	$162
1601667	Residual Solvent Class 2 - Methylbutylketone (1.2 mL/ampule; 3 ampules)	F0D202	$162
1601689	Residual Solvent Class 2 - Methylcyclohexane (1.2 mL/ampule; 3 ampules)	F0D044	$162
1601441	Residual Solvent Class 2 - Methylene Chloride (1.2 mL/ampule; 3 ampules)	F0D046	$162
1601703	Residual Solvent Class 2 - N-Methylpyrrolidone (1.2 mL/ampule; 3 ampules)	F0D183	$162
1601725	Residual Solvent Class 2 - Nitromethane (1.2 mL/ampule; 3 ampules)	F0D210	$162
1601747	Residual Solvent Class 2 - Pyridine (1.2 mL/ampule; 3 ampules)	F0D215	$162
1601769	Residual Solvent Class 2 - Sulfolane (1.2 mL/ampule; 3 ampules)	F0D187	$162
1601770	Residual Solvent Class 2 - Tetrahydrofuran (1.2 mL/ampule; 3 ampules)	F0D043	$162
1601780	Residual Solvent Class 2 - Tetralin (1.2 mL/ampule; 3 ampules)	F0D228	$162
1601805	Residual Solvent Class 2 - Toluene (1.2 mL/ampule; 3 ampules)	F0D042	$162

New Items at a Glance (*Continued*)

Cat. No.	Description	Curr. Lot	Price
1601827	Residual Solvent Class 2 - Trichloroethylene (1.2 mL/ampule; 3 ampules)	F0D221	$162
1601849	Residual Solvent Class 2 - Xylenes (1.2 mL/ampule; 3 ampules)	F0D041	$162
1612594	Sevoflurane Related Compound C (0.2 mL)	F0D142	$506
1613407	Sodium Acetate (1 g) (AS)	F0D083	$162
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	$162
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	$162
1613804	Sodium Chloride (1 g) (AS)	F0D269	$162
1613859	Sodium Citrate (1 g) (AS)	F0D172	$162
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	$162
1614454	Sodium Nitrite (1 g) (AS)	F0D117	$162
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	$162
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	$162
1667585	Titanium Dioxide (1 g) (AS)	F0D079	$162
1670207	Tolcapone (200 mg)	F0D280	$162
1670218	Tolcapone Related Compound A (25 mg)	F0D282	$506
1708762	Valsartan (350 mg)	F0C147	$162
1724747	Zinc Oxide (2 g) (AS)	F0D170	$162
1724769	Zinc Sulfate (1 g) (AS)	F0D133	$162

USING 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. As a service to our customers, labeled purity values for Reference Standards and Authentic substances released after January 1, 2004 are listed in this catalog. See p. 7 for explanation of how values are calculated.

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. 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 1,660 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 8–57 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through October 2004. 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 28–NF 23*. Individual *USP* or *NF* monographs specify the USP Reference Standard(s) required for assay and test procedures. The *USP 28–NF 23* 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.

USING USP REFERENCE STANDARDS

- The user must determine the suitability of Reference Standards for applications and uses not in the *USP–NF*.

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 28–NF 23* 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.

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- 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.

USING USP REFERENCE STANDARDS

- The user must determine the suitability of Reference Standards for applications and uses not in the *USP–NF*.

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 28–NF 23* 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

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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 (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 3 (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 4 (Purity Values) Assigned purity value as it appears on the RS or AS label. Code interpretations for the basis of purity assignments are as follows:

Basis Code	Interpretation
(ai)	as is
(dr)	dried
(an)	anhydrous
(fb)	free base
(ig)	ignited

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the **Nov.–Dec. 2004,** 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): Lot designations for recent lots no longer being distributed. The indicated month and year 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) List 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.

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1027302	Amiodarone Hydrochloride (200 mg)	F0D257	0.995 mg/mg (ai)	1		[19774-82-4]	$162
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	100.0 % (ai)	1		[7783-28-0]	$162
1087359	Calcium Stearate (2 g) (AS)	F0D255	9.8% CaO (ai)	1		[1592-23-0]	$162
1179650	Dextran T-10 (200 mg)	F0D238	1.000 mg/mg (dr)	1		[9004-54-0]	$162
1187091	Dibutyl Sebacate (1 mL)	F0D128	99.2% (ai)	1		[109-43-3]	$162
1270377	Fexofenadine Hydrochloride (200 mg)	F0D244	0.996 mg/mg (ai)	1		[138452-21-8]	$162
1270388	Fexofenadine Related Compound A (25 mg) (4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-alpha,alpha-dimethyl benzeneacetic acid)	F0D245	0.99 mg/mg (ai)	1		n/f	$506
1270399	Fexofenadine Related Compound B (25 mg) (3-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid hydrochloride)	F0D246		1		n/f	$506
1271700	Fluconazole (200 mg)	F0D262	1.00 mg/mg (ai)	1		[86386-73-4]	$162
1271711	Fluconazole Related Compound A (10 mg) (2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D080	0.95 mg/mg (ai)	1		n/f	$506
1271722	Fluconazole Related Compound B (10 mg) (2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D081	0.92 mg/mg (ai)	1		[81886-51-3]	$506
1335279	Hypromellose Acetate Succinate (100 mg)	F0D275		1		[71138-97-1]	$162
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	88.5% (ai)	1		[50-21-5]	$162
1370462	Losartan Potassium (250 mg)	F0D287	0.998 mg/mg (ai)	1		[124750-99-8]	$162
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	41.8% MgO (ai)	1		[546-93-0]	$162
1374340	Magnesium Stearate (5 g) (AS)	F0D214	65% Stearate 29% Palmitate 4.8% Mg (ai)	1		[577-04-0]	$162
1375069	Mangafodipir Trisodium (200 mg)	F0D272	0.996 mg/mg (an)	1		[140678-14-4]	$162
1375070	Mangafodipir Related Compound A (15 mg) (manganese (II) dipyridoxyl monophosphate sodium salt)	F0D266		1		n/f	$506
1375080	Mangafodipir Related Compound B (15 mg) (manganese (II) dipyridoxyl diphosphate mono-overalkylated sodium salt)	F0D267		1		n/f	$506
1478254	Olive Oil (1 g) (AS)	F0D175		1		[8001-25-0]	$162
1500557	Peanut Oil (1 g) (AS)	F0D171		1		[8002-03-7]	$162
1526200	Phenoxyethanol (500 mg)	F0D069	0.998 mg/mg (ai)	1		[122-99-6]	$162
1548407	Potassium Sorbate (1 g) (AS)	F0D264	99.6% (dr)	1		[24634-61-5]	$162
1612594	Sevoflurane Related Compound C (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-propanol)	F0D142	1.00 mg/mg (ai)	1		[920-66-1]	$506
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	99.7% (dr)	1		[144-55-8]	$162
1613804	Sodium Chloride (1 g) (AS)	F0D269	100.0% (ai)	1		[7647-14-5]	$162
1670207	Tolcapone (200 mg)	F0D280	0.999 mg/mg (ai)	1		[134308-13-7]	$162
1670218	Tolcapone Related Compound A (25 mg) (4'-methyl-3,4-dihydroxybenzophenone)	F0D282		1		n/f	$506
1021000	Aminocaproic Acid (200 mg)	G0D101	0.997 mg/mg (dr)	2	F-4 (09/05)	[60-32-2]	$162
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272		2	F-1 (10/05)	[5411-22-3]	$215
1068004	Betamethasone Sodium Phosphate (500 mg)	K0C358	0.993 mg/mg (an)	2	J0B043 (06/05) I-1 (02/03) I (01/01)	[151-73-5]	$162
1107503	Chloramphenicol Palmitate Polymorph A (100 mg)	G1D219		2,3	G (10/05) F (08/99)	[530-43-8]	$506

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1119309	Chlorthalidone Related Compound A (15 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)	H0D251	1.00 mg/mg (ai)	2,3	G0C376 (09/05) F-3 (07/04)	n/f	$506
1147009	Colistimethate Sodium (200 mg)	H1D234	0.420 mg/mg (dr)	2	H (09/05)	[8068-28-8]	$162
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	0.997 mg/mg (dr)	2	H (09/05) G (03/01)	[5965-13-9]	$215
1204000	Dihydrotachysterol (30 mg/ampule; 4 ampules)	J0D250	0.996 mg/mg (ai)	2	I (06/05)	[67-96-9]	$162
1224802	Docusate Sodium (500 mg)	K0D134	0.988mg/mg (an)	2	J (09/05) I-1 (05/02)	[577-11-7]	$162
1277274	Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz)	G0D270		2	F (06/05)	n/f	$506
1279000	Fluorouracil (250 mg)	H2D190	1.000 mg/mg (dr)	2	H-1 (09/05) H (01/02)	[51-21-8]	$162
1378001	Medroxyprogesterone Acetate (200 mg)	I0D013	0.995 mg/mg (ai)	2	H-2 (09/05) H-1 (04/03)	[71-58-9]	$162
1396309	Metformin Hydrochloride (200 mg)	G0D271	0.999 mg/mg (ai)	2	F0C209 (08/05)	[1115-70-4]	$189
1397006	Methacycline Hydrochloride (200 mg)	I0C348	903 ug/mg (ai)	2	H (10/05) G (04/01)	[3963-95-9]	$162
1469005	Norethindrone (200 mg)	K0C307	0.998 mg/mg (ai)	2	J1B065 (09/05) J-1 (05/03) J (07/02) I-1 (03/01)	[68-22-4]	$162
1477003	Nystatin (200 mg)	O0D177	5751 Nystatin units/mg (dr)	2	N1B004 (09/05) N (01/03)	[1400-61-9]	$162
1554002	Pramoxine Hydrochloride (500 mg)	I1D197	0.998 mg/mg (dr)	2	I (10/05) H (11/02)	[637-58-1]	$162
1602003	Resorcinol (200 mg)	I0D135	0.998 mg/mg (ai)	2	H-1 (10/05) H (04/01)	[108-46-3]	$162
1606503	Rutin (100 mg)	G0C355		2	F (09/05)	[153-18-4]	$162
1626001	Sulfadimethoxine (200 mg)	G0D249	0.998 mg/mg (ai)	2	F4C298 (09/05) F-3 (11/04) F-2 (03/99)	[122-11-2]	$162
1626500	Sulfadoxine (200 mg)	F3C336	0.999 mg/mg (ai)	2	F-2 (10/05) F-1 (07/02)	[2447-57-6]	$162
1661002	Thiopental **CIII** (250 mg)	I1D198	1.000mg/mg (dr)	2	I (09/05)	[76-75-5]	$215
1683606	Triethyl Citrate (500 mg)	G0C393		2	F-1 (10/05) F (03/02)	[77-93-0]	$162

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1000601	Acebutolol Hydrochloride (125 mg)	F-1				[34381-68-5]	$162
1001003	Acenocoumarol (200 mg)				F (10/05)	[152-72-7]	$162
1001502	Acepromazine Maleate (250 mg)	F-2			F-1 (05/02)	[3598-37-6]	$162
1002505	Acesulfame Potassium (200 mg)	F0C136				[55589-62-3]	$270
1003009	Acetaminophen (400 mg)	J-1			J (05/02) I (05/99)	[103-90-2]	$129
1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)	M0A029			L (06/04) K (02/00)	[103-84-4]	$78
1005004	Acetazolamide (2 g)	J				[59-66-5]	$162
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	99.9% (ai)			[64-19-7]	$162
1006007	Acetohexamide (250 mg)	H			G-1 (06/99)	[968-81-0]	$162
1006506	Acetohydroxamic Acid (200 mg)	F-1			F (03/03)	[546-88-3]	$162
1007000	Acetophenazine Maleate (200 mg)	F-1				[5714-00-1]	$162
1008501	Acetylcholine Chloride (200 mg)	G				[60-31-1]	$162
1009005	Acetylcysteine (200 mg)	H1B169			H (01/04)	[616-91-1]	$162
1009901	Acetyltributyl Citrate (500 mg)	G0C120			F (05/04)	[77-90-7]	$162
1009923	Acetyltriethyl Citrate (500 mg)	F-1			F (05/02)	[77-89-4]	$162
1012065	Acyclovir (300 mg)	J0C149			I (06/04)	[59277-89-3]	$205
1012101	Adenine (200 mg)	G-1			G (06/00)	[73-24-5]	$162
1012123	Adenosine (200 mg)	G0C295			F1B058 (01/05) F (04/03)	[58-61-7]	$162
1012145	Agigenin (25 mg)	F				n/f	$506
1012509	L-Alanine (200 mg)	F-2			F-1 (04/01)	[56-41-7]	$162
1012553	Albendazole (200 mg)	G			F-1 (01/00)	[54965-21-8]	$162
1012600	Albuterol (200 mg)	I			H (12/00)	[18559-94-9]	$162
1012633	Albuterol Sulfate (200 mg)	J			I (04/00)	[51022-70-9]	$162
1012757	Alclometasone Dipropionate (300 mg)	H			G (01/00)	[66734-13-2]	$162
1012768	Alcohol (1.2 mL/ampule; 5 ampules)	F0D030				[64-17-5]	$162
1012772	Dehydrated Alcohol (1.2 mL/ampule; 5 ampules)	F0D031				[64-17-5]	$162
1012699	Alcohol Determination–Acetonitrile (5 mL/ampule; 5 ampules)	F0C419	2% v/v (ai)			n/f	$162
1012688	Alcohol Determination–Alcohol (5 mL/ampule; 5 ampules)	F0C399	1.96% v/v (ai)			n/f	$162
1012780	Alendronate Sodium (200 mg)	F0B315				[121268-17-5]	$162
1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016				[70879-28-6]	$215
1012939	Allantoin (200 mg)	F0C169				[97-59-6]	$162
1012950	Alliin (25 mg)	F				[556-27-4]	$1,586
1013002	Allopurinol (250 mg)	J0C186			I-1 (01/05) I (07/02)	[315-30-0]	$162
1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)	G			F-3 (05/02) F-2 (04/99)	n/f	$506
1013057	S-Allyl-L-Cysteine (25 mg)	F				n/f	$506
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F				[561-78-4]	$215
1015008	Alprazolam **CIV** (200 mg)	H1C133			H (06/05)	[28981-97-7]	$215
1016000	Alprostadil (25 mg)	H				[745-65-3]	$1,586
1017105	Altretamine (500 mg)	F				[645-05-6]	$162
1017502	Dried Aluminum Hydroxide Gel (200 mg)	F2B120			F-1 (01/04)	[21645-51-2]	$162
1018505	Amantadine Hydrochloride (200 mg)	H			G (04/01)	[665-66-7]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1019202	Amcinonide (200 mg)	G0B260			F-1 (03/04)	[51022-69-6]	$162
1019417	Amifostine Disulfide (25 mg)	F0C152				[112901-68-5]	$506
1019508	Amikacin (200 mg)	I			H (08/00)	[37517-28-5]	$162
1019701	Amiloride Hydrochloride (500 mg)	H				[17440-83-4]	$162
1019756	Aminobenzoate Potassium (200 mg)	F-1			F (06/01)	[138-84-1]	$162
1019767	Aminobenzoate Sodium (200 mg)	F				[55-06-6]	$162
1019803	Aminobenzoic Acid (200 mg) (p-aminobenzoic acid)	H1C083			H (10/04) G (10/00)	[150-13-0]	$162
1020008	Aminobutanol (500 mg)	G-1			G (06/99)	[96-20-8]	$405
1021000	Aminocaproic Acid (200 mg)	G0D101	0.997 mg/mg (dr)	2	F-4 (09/05)	[60-32-2]	$162
1021703	N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine (25 mg)	F-1				n/f	$506
1022808	2-Amino-5-chlorobenzophenone (25 mg)	I			H-1 (01/03)	[719-59-5]	$506
1025205	Aminoglutethimide (200 mg)	F				[125-84-8]	$162
1025307	m-Aminoglutethimide (100 mg)	G			F (05/01)	n/f	$506
1025351	Aminohippuric Acid (200 mg)	F-1				[61-78-9]	$162
1025806	2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-d-glucose (25 mg)	F				n/f	$506
1025908	Aminopentamide Sulfate (200 mg)	F0B273				[60-46-8]	$162
1026004	m-Aminophenol (300 mg)	F				[591-27-5]	$506
1026401	Aminosalicylic Acid (125 mg)	F-1			F (03/99)	[65-49-6]	$129
1026605	3-Amino-2,4,6-triiodobenzoic Acid (50 mg)	G				[3119-15-1]	$506
1027007	5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid (50 mg)	F-1				[2280-89-9]	$506
1027302	Amiodarone Hydrochloride (200 mg)	F0D257	0.995 mg/mg (ai)	1		[19774-82-4]	$162
1028000	Amitraz (200 mg)	F0C042				[33089-61-1]	$162
1029002	Amitriptyline Hydrochloride (200 mg)	J0A004			I (03/03)	[549-18-8]	$162
1029501	Amlodipine Besylate (200 mg)	F0D167	0.996 mg/mg (ai)			[111470-99-6]	$162
1029909	Ammonio Methacrylate Copolymer Type A (100 mg)	F-1			F (06/01)	[33434-24-1]	$162
1029910	Ammonio Methacrylate Copolymer Type B (100 mg)	F2C082			F-1 (06/05) F (05/00)	[33434-24-1]	$162
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	33.3% NH3 (ai)			[8000-73-5}	$162
1029953	Ammonium Chloride (200 mg)	F0C134				[12125-02-9]	$162
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	100.0 % (ai)	1		[7783-28-0]	$162
1030001	Amobarbital **CII** (200 mg)	F-2				[57-43-2]	$215
1031004	Amodiaquine Hydrochloride (500 mg)	H0B238			G-1 (04/03)	[6398-98-7]	$162
1031401	Amoxapine (200 mg)	G			F-1 (04/02)	[14028-44-5]	$162
1031503	Amoxicillin (200 mg)	J0C043			I (07/04)	[61336-70-7]	$162
1032007	Amphotericin B (125 mg)	J3C246	1009 ug/mg (dr)		J-2 (01/05) J-1 (07/02)	[1397-89-3]	$129
1033000	Ampicillin (200 mg)	J-1			J (12/01)	[69-53-4]	$162
1033203	Ampicillin Sodium (125 mg)	G-1			G (10/99)	[69-52-3]	$129
1033407	Ampicillin Trihydrate (200 mg)	G1D147			G (08/05)	[7177-48-2]	$162
1034002	Amprolium (200 mg)	G0C317	0.991 mg/mg (dr)		F-1 (04/05) F (04/02)	[121-25-5]	$162
1034308	Amrinone (500 mg)	G				[60719-84-8]	$162
1034320	Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one)	F				[62749-46-6]	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1034341	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	$506
1034363	Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile)	F-1			F (05/00)	n/f	$506
1036008	Anileridine Hydrochloride **CII** (250 mg)	F				[126-12-5]	$215
1036507	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg)	G-1				[30078-48-9]	$506
1038003	Antazoline Phosphate (200 mg)	H			G-1 (04/02)	[154-68-7]	$162
1039006	Anthralin (200 mg)	I0B221			H (11/02)	[1143-38-0]	$162
1040005	Antipyrine (200 mg)	G			F-4 (09/01)	[60-80-0]	$162
1040708	Apigenin-7-glucoside (30 mg)	F				n/f	$506
1041008	Apomorphine Hydrochloride (250 mg)	H			G (01/03)	[41372-20-7]	$168
1041609	Apraclonidine Hydrochloride (100 mg)	H0B112			G (06/03)	[73218-79-8]	$498
1042000	Aprobarbital **CIII** (200 mg) (AS)	F-1				[77-02-1]	$215
1042500	L-Arginine (200 mg)	G-1			G (09/00)	[74-79-3]	$162
1042601	Arginine Hydrochloride (125 mg)	G0B060			F-1 (05/03)	[1119-34-2]	$129
1042703	Arsanilic Acid (25 mg)	F				[98-50-0]	$162
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012			P (04/03)	[50-81-7]	$162
1043706	Aspartame (200 mg)	H1B125			H (05/03)	[22839-47-0]	$162
1043750	Aspartame Acesulfame (200 mg)	F0C137				[106372-55-8]	$162
1043728	Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)	H			G-1 (10/99)	[5262-10-2]	$506
1043819	Aspartic Acid (100 mg)	F0B087				[6899-03-2]	$162
1044006	Aspirin (500 mg)	H			G-1 (11/02)	[50-78-2]	$162
1044301	Astemizole (200 mg)	F				[68844-77-9]	$162
1044403	Atenolol (200 mg)	H1C320	998 ug/mg (dr)		H (01/05) G (08/01)	[29122-68-7]	$162
1044651	Atovaquone (200 mg)	F0B190				[95233-18-4]	$162
1044662	Atovaquone Related Compound A (25 mg) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone)	F0B188				n/f	$506
1044800	Atracurium Besylate (100 mg)	F0B143				[64228-81-5]	$162
1045009	Atropine Sulfate (500 mg)	M0B098			L-2 (04/03) L-1 (06/02) L (10/00)	[5908-99-6]	$162
1045337	Avobenzone (500 mg)	G0B280			F (09/03)	[70356-09-1]	$162
1045508	Aurothioglucose (100 mg)	H0B224			G (10/03) F (12/01)	[12192-57-3]	$270
1045600	Azaerythromycin A (100 mg)	G			F-1 (02/02) F (02/99)	[76801-85-9]	$506
1045756	Azaperone (200 mg)	F				[1649-18-9]	$162
1045803	Azatadine Maleate (200 mg)	G0B300			F-1 (04/04) F (06/00)	[3978-86-7]	$162
1046001	Azathioprine (200 mg)	H			G-1 (02/00)	[446-86-6]	$162
1046056	Azithromycin (100 mg)	H0C212			G (11/04) F (06/00)	[117772-70-0]	$162
1046103	Azlocillin Sodium (200 mg)	F				[37091-65-9]	$162
1046147	Azo-aminoglutethimide (100 mg)	F				n/f	$506
1046205	Aztreonam (200 mg)	G0C077			F-1 (03/04)	[78110-38-0]	$162
1046307	Aztreonam E-Isomer (50 mg)	F1D056			F (04/05)	n/f	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1046409	Open Ring Aztreonam (25 mg)	G0D071			F (12/04)	[87500-74-1]	$506
1047300	Bacampicillin Hydrochloride (200 mg)	G0B053			F (11/02)	[37661-08-8]	$162
1047503	Bacitracin (1 g) (Susceptibility disk standard)	G1C254			G (07/04)	[1405-87-4]	$162
1048007	Bacitracin Zinc (200 mg)	N0A024			M-1 (11/02) M (02/00)	[1405-89-6]	$162
1048200	Baclofen (500 mg)	I				[1134-47-0]	$162
1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)	H1C289			H (11/04)	n/f	$506
1048506	Beclomethasone Dipropionate (200 mg)	K			J (12/00)	[5534-09-8]	$162
1048619	Benazepril Hydrochloride (125 mg)	F0C250				[86541-74-4]	$162
1048620	Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C252				n/f	$506
1048630	Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C256				n/f	$506
1048641	Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine]-1-acetic acid)	F0C425	1.00 mg/mg (ai)			[86541-78-8]	$506
1049000	Bendroflumethiazide (200 mg)	H0C402	0.994 mg/mg (ai)		G-1 (06/05)	[73-48-3]	$162
1050009	Benoxinate Hydrochloride (200 mg)	F-2			F-1 (10/99)	[5987-82-6]	$129
1051001	Benzalkonium Chloride (5 mL of approx. 10% aqueous solution)	K0B151			J (06/03)	[8001-54-5]	$162
1054000	Benzocaine (500 mg)	J0C130			I (12/04)	[94-09-7]	$162
1055002	Benzoic Acid (300 mg)	F6B173			F-5 (03/04) F-4 (07/01)	[65-85-0]	$162
1056005	Benzonatate (1 g)	I0B003			H (01/03)	[104-31-4]	$162
1056504	1,4-Benzoquinone (200 mg)	G1B145			G (01/04) F-1 (11/01) F (09/00)	[106-51-4]	$162
1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)	H0B069			G-4 (03/03)	[121-30-2]	$506
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272		2	F-1 (10/05)	[5411-22-3]	$215
1060002	Benzthiazide (200 mg)	F				[91-33-8]	$162
1061005	Benztropine Mesylate (200 mg)	I0C038			H (09/04)	[132-17-2]	$162
1061901	Benzyl Alcohol (500 mg/ampule)	G0B306			F0B106 (10/03)	[100-51-6]	$162
1062008	Benzyl Benzoate (5 g)	J0C060			I (05/04)	[120-51-4]	$162
1064003	1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride (25 mg)	F-1				n/f	$506
1065006	Bephenium Hydroxynaphthoate (500 mg)	F				[3818-50-6]	$162
1065618	Betahistine Hydrochloride (200 mg)	F0C105				[5579-84-0]	$162
1065709	Betaine Hydrochloride (200 mg)	F-1			F (11/02)	[590-46-5]	$162
1066009	Betamethasone (200 mg)	K2C204			K-1 (10/04) K (11/02)	[378-44-9]	$162
1067001	Betamethasone Acetate (500 mg)	J0B079			I (08/03)	[987-24-6]	$162
1067307	Betamethasone Benzoate (200 mg)	F-1				[22298-29-9]	$162
1067704	Betamethasone Dipropionate (125 mg)	K0C229			J (04/04) I (03/99)	[5593-20-4]	$129

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1068004	Betamethasone Sodium Phosphate (500 mg)	K0C358	0.993 mg/mg (an)	2	J0B043 (06/05) I-1 (02/03) I (01/01)	[151-73-5]	$162
1069007	Betamethasone Valerate (200 mg)	K0C330	0.997 mg/mg (ai)		J (07/05) I (05/00)	[2152-44-5]	$162
1069903	Betaxolol Hydrochloride (200 mg)	G			F-1 (06/00)	[63659-19-8]	$162
1070006	Betazole Hydrochloride (200 mg)	H				[138-92-1]	$162
1071009	Bethanechol Chloride (200 mg)	G1D088	1.00 mg/mg (dr)		G (03/05) F-3 (07/01)	[590-63-6]	$162
1071304	Bile Salts (10 g)	I0C003			H-1 (05/04) H (05/99)	[145-42-6]	$129
1071439	Positive Bioreaction (3 strips; 10 cm x 1 cm)	F0D014				n/f	$338
1071508	Biotin (200 mg)	H1B019			H (04/03)	[58-85-5]	$162
1072001	Biperiden (200 mg)	F2B080			F-1 (02/04)	[514-65-8]	$162
1073004	Biperiden Hydrochloride (200 mg)	F-3			F-2 (06/99)	[1235-82-1]	$162
1074007	Bisacodyl (125 mg)	I1B162			I (01/04) H-1 (02/99)	[603-50-9]	$129
1074700	2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine (25 mg)	F				n/f	$506
1075203	Bis(2-ethylhexyl)maleate (250 mg)	F-2			F-1 (01/01)	[142-16-5]	$506
1075509	p-Bis(di-n-propyl)carbamylbenzenesulfonamide (50 mg)	F				n/f	$506
1075531	Bismuth Citrate (100 mg)	F				[813-93-4]	$162
1075553	Bismuth Subsalicylate (100 mg)	F1C394			F (08/05)	[14882-18-9]	$162
1075757	Bisoprolol Fumarate (200 mg)				F0B038 (08/05)	[104344-23-2]	$162
1076002	4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone (25 mg)				G (05/03)	n/f	$506
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086				[84776-26-1]	$541
1076308	Bleomycin Sulfate (15 mg)	J0B213			I (01/04)	[9041-93-4]	$319
1076341	Boric Acid (1 g) (AS)	F0D036	100.0% (dr)			[10043-35-3]	$208
1076352	Bretylium Tosylate (200 mg)	F-1				[61-75-6]	$162
1076363	Brinzolamide (200 mg)	F0C034				[138890-62-7]	$162
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	$506
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	$506
1076501	Bromocriptine Mesylate (150 mg)	I1C197			I (09/04)	[22260-51-1]	$162
1077005	Bromodiphenhydramine Hydrochloride (200 mg)	F-1				[1808-12-4]	$162
1077708	8-Bromotheophylline (400 mg)	G			F (07/02)	[10381-75-6]	$458
1078008	Brompheniramine Maleate (125 mg)	I1A036			I (01/03) H-1 (04/99)	[980-71-2]	$129
1078303	Bumetanide (250 mg)	I0C111			H0B030 (05/04) G (03/03)	[28395-03-1]	$162
1078325	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2			F-1 (05/00)	n/f	$506
1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2			F-1 (01/03)	[28328-53-2]	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1078507	Bupivacaine Hydrochloride (1 g)	H			G-2 (03/03) G-1 (08/02)	[14252-80-3]	$162
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	F-1			F (02/99)	[53152-21-9]	$215
1078711	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			F (04/04)	n/f	$506
1078733	Bupropion Hydrochloride (200 mg)	F0C123				[31677-93-7]	$216
1078802	Buspirone Hydrochloride (200 mg)	H0B301			G (05/05)	[33386-08-2]	$162
1079000	Butabarbital **CIII** (200 mg)	H0C007			G (03/04)	[125-40-6]	$215
1080000	Butacaine Sulfate (600 mg)	F				[149-15-5]	$162
1081002	Butalbital **CIII** (200 mg)	H0C054			G2B077 (07/04) G-2 (06/03) G (05/02)	[77-26-9]	$215
1081501	Butamben (200 mg)	F				[94-25-7]	$162
1082300	Butoconazole Nitrate (200 mg)	F1B097			F (03/03)	[64872-77-1]	$162
1082504	Butorphanol Tartrate **CIV** (500 mg)	J			I (06/00)	[58786-99-5]	$215
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	>99.0% (ai)			[128-37-0]	$162
1082800	Monotertiary-butyl-p-benzoquinone (100 mg) (FCC)	F				[3602-55-9]	$162
1082901	Butyl 3-(butylamino)-4-phenoxy-5-sulfamoyl-benzoate (25 mg)	F-1				n/f	$506
1083008	2-*tert*-Butyl-4-hydroxyanisole (200 mg)	L0C028			K (09/03)	[88-32-4]	$162
1083100	3-*tert*-Butyl-4-hydroxyanisole (200 mg)	K0C239			J (03/05) I-1 (09/01)	[121-00-6]	$162
1084000	Butylparaben (200 mg)	I0C139			H-1 (03/04) H (09/01)	[94-26-8]	$162
1085003	Caffeine (200 mg)	J			I (06/02)	[58-08-2]	$162
1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)	J0B204			I (03/04)	[58-08-2]	$96
1086108	Calcifediol (75 mg)	G				[63283-36-3]	$506
1086334	Calcium Acetate (1 g) (AS)	F0D156	100.0% (an)			[62-54-4]	$162
1086356	Calcium Ascorbate (200 mg)	F-1			F (08/01)	[5743-28-2]	$162
1086403	Calcium Carbonate (1 g) (AS)	F0D099	99.1% (dr)			[471-34-1]	$162
1086436	Calcium Chloride (1 g) (AS)	F0D153	101.9% (ai)			[10035-04-8]	$162
1086800	Calcium Gluceptate (200 mg)	F-1			F (09/00)	[29039-00-7]	$162
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	98.1% (ai)			[1305-62-0]	$162
1086902	Calcium Lactobionate (200 mg)	G0B138			F-1 (01/04) F (11/01)	[110638-68-1]	$162
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	0.990 mg/mg (dr)		N-1 (06/05) N (06/00)	[137-08-6]	$162
1087202	Calcium Saccharate (200 mg)	F				[5793-89-5]	$162
1087359	Calcium Stearate (2 g) (AS)	F0D255	9.8% CaO (ai)	1		[1592-23-0]	$162
1087406	Calcium Sulfate (1 g) (AS)	F0D236	100.0% (dr)			[10101-41-4]	$162
1087701	Candelilla Wax (250 mg)	F0D123				[8006-44-8]	$162
1088001	Candicidin (200 mg)	F				[1403-17-4]	$162
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2				[13956-29-1]	$506
1090003	Cannabinol **CI** (25 mg) (AS)				F-2 (05/02)	[521-35-7]	$215
1091006	Capreomycin Sulfate (200 mg)	G			F (06/01)	[1405-37-4]	$162
1091505	Caprylocaproyl Polyoxylglycerides (200 mg)	F0C312				n/f	$182

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1091108	Capsaicin (100 mg)	G2D136	0.985 mg/mg (dr)		G-1 (07/05) G (03/02) F-1 (06/00) F (03/99)	[404-86-4]	$162
1091200	Captopril (200 mg)	H				[62571-86-2]	$162
1091221	Captopril Disulfide (100 mg)	G1B066			G (01/04)	[64806-05-9]	$506
1092009	Carbachol (200 mg)	G				[51-83-2]	$162
1093001	Carbamazepine (100 mg)	J			I-1 (02/00)	[298-46-4]	$162
1093205	Carbarsone (200 mg)	F				[121-59-5]	$162
1093500	Carbenicillin Indanyl Sodium (300 mg)	G				[26605-69-6]	$162
1094004	Carbenicillin Monosodium Monohydrate (200 mg)	G-2				n/f	$162
1095506	Carbidopa (400 mg)	I			H (10/99)	[38821-49-7]	$162
1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)	H0B121			G (04/03)	n/f	$506
1096000	Carbinoxamine Maleate (200 mg)	H			G-1 (11/02)	[3505-38-2]	$162
1096407	Carboplatin (100 mg)	H0C240			G (07/04) F (03/00)	[41575-94-4]	$165
1096509	Carboprost Tromethamine (25 mg)	F-1			F (02/01)	[58551-69-2]	$506
1096600	Carisoprodol (1 g)	G			F-2 (05/02)	[78-44-4]	$162
1096757	Carteolol Hydrochloride (200 mg)	F-1			F (11/00)	[51781-21-6]	$162
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I				[76333-53-4]	$582
1096906	Cefaclor (400 mg)	H				[70356-03-5]	$162
1096917	Cefaclor, Delta-3-Isomer (30 mg)	G			F-1 (02/00)	n/f	$506
1097104	Cefadroxil (125 mg)	I1B319	935 ug/mg (ai)		I (01/05) H (04/99)	[66592-87-8]	$129
1097308	Cefamandole Lithium (200 mg)	H				n/f	$162
1097400	Cefamandole Nafate (200 mg)	H				[42540-40-9]	$162
1097501	Cefamandole Sodium (250 mg)	F				[30034-03-8]	$162
1097603	Cefazolin (400 mg)	L0C345			K (04/05) J (06/00)	[25953-19-9]	$162
1097636	Cefepime Hydrochloride (500 mg)	G0D116	860 ug/mg (an)		F0C063 (06/05)	[123171-59-5]	$162
1097647	Cefepime Hydrochloride System Suitability (25 mg)	F0C095				n/f	$506
1097658	Cefixime (500 mg)	F				[79350-37-1]	$162
1097771	Cefmenoxime Hydrochloride (350 mg)	F				[75738-58-8]	$162
1097782	Cefmetazole (200 mg)	F-1			F (04/02)	[56796-20-4]	$162
1097750	Cefonicid Sodium (1 g)	H0D105	887 ug/mg (an)		G (06/05)	[61270-78-8]	$162
1097705	Cefoperazone Dihydrate (200 mg)	H			G (12/99)	[62893-19-0]	$162
1097807	Ceforanide (200 mg)	F-1			F (07/00)	[60925-61-3]	$162
1097909	Cefotaxime Sodium (250 mg)	J0C189	901 ug/mg (ai)		I (11/04)	[64485-93-4]	$129
1097975	Cefotetan (500 mg)	H0C175			G (07/04) F (09/00)	[69712-56-7]	$162
1098005	Cefotiam Hydrochloride (325 mg)	G0B050			F (01/03)	[66309-69-1]	$162
1098107	Cefoxitin (500 mg)	I			H (05/00)	[35607-66-0]	$162
1098118	Cefpiramide (300 mg)	F0C203				[70797-11-4]	$162
1098027	Cefpodoxime Proxetil (350 mg)	F0C192	736 ug/mg (an)			[87239-81-4]	$162
1098049	Cefprozil E-Isomer (50 mg)				F2C284 (08/05) F-1 (10/04) F (05/01)	[121123-17-9]	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1098050	Cefprozil Z-Isomer (200 mg)	G0C037			F (12/03)	[121123-17-9]	$162
1098129	Ceftazidime, Delta-3-Isomer (25 mg)	G			F (03/00)	n/f	$506
1098130	Ceftazidime Pentahydrate (300 mg)	H			G (12/99)	[78439-06-2]	$162
1098173	Ceftizoxime (200 mg)	H				[68401-81-0]	$162
1098184	Ceftriaxone Sodium (350 mg)	G0B264			F (08/03)	[104376-79-6]	$162
1098195	Ceftriaxone Sodium E-Isomer (25 mg)	I0C190			H (07/04) G (08/01) F-1 (02/00)	n/f	$506
1098209	Cefuroxime Sodium (200 mg)	H			G-1 (05/00)	[56238-63-2]	$162
1098220	Cefuroxime Axetil (500 mg)	G			F-1 (05/02)	[64544-07-6]	$162
1098231	Cefuroxime Axetil Delta-3-Isomers (35 mg)	H0B160			G (03/03)	n/f	$506
1098322	Cellaburate (350 mg) (Cellulose Acetate Butyrate)	F0D220				[9004-36-8]	$162
1098300	Cellulose Acetate (125 mg)	F-1			F (11/99)	[9004-35-7]	$129
1098355	Cellulose Acetate Phthalate (125 mg)	F-1			F (03/99)	[9004-38-0]	$129
1098708	Cephaeline Hydrobromide (200 mg)	G-1				n/f	$506
1099008	Cephalexin (250 mg)	I-2			I-1 (03/00)	[23325-78-2]	$162
1102000	Cephalothin Sodium (200 mg)	I				[58-71-9]	$162
1102408	Cephapirin Benzathine (100 mg)	F				[97468-37-6]	$162
1102500	Cephapirin Sodium (200 mg)	I-1			I (07/02)	[24356-60-3]	$162
1102805	Cephradine (200 mg)	J			I (04/00)	[58456-86-3]	$162
1103003	Cetyl Alcohol (100 mg)	I			H (03/99)	[36653-82-4]	$162
1103105	Cetyl Palmitate (50 mg)	F0B241				[540-10-3]	$162
1104006	Cetylpyridinium Chloride (500 mg)				I (10/05) H-1 (06/01) H (08/99)	[6004-24-6]	$162
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406				[91722-47-3]	$541
1106001	Chlorambucil (125 mg) (FOR U.S. SALE ONLY)	G			F-1 (02/99)	[305-03-3]	$129
1107004	Chloramphenicol (200 mg)	N1C074			N (10/04) M (03/00)	[56-75-7]	$162
1107300	Chloramphenicol Palmitate (200 mg)	G-1				[530-43-8]	$162
1107401	Chloramphenicol Palmitate Nonpolymorph A (200 mg)	F-1				[530-43-8]	$506
1107503	Chloramphenicol Palmitate Polymorph A (100 mg)	G1D219		2,3	G (10/05) F (08/99)	[530-43-8]	$506
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063			H-1 (03/03)	[58-25-3]	$215
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4				[438-41-5]	$215
1110020	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]	$506
1111001	Chlorhexidine (200 mg)	F0C306				[55-56-1]	$162
1111103	Chlorhexidine Acetate (500 mg)	F0C281				[56-95-1]	$162
1111307	Chlorhexidine Related Compounds (50 mg)	F0D017				n/f	$506
1112503	Chlorobutanol (200 mg)				G (09/05) F-3 (12/01)	[6001-64-5]	$162
1115545	Chlorogenic Acid (50 mg)	F0C420	0.97 mg/mg (ai)			[327-97-9]	$162
1115556	beta-Chlorogenin (20 mg)	F				n/f	$506
1117008	Chloroprocaine Hydrochloride (200 mg)	G0B285			F-3 (01/04) F-2 (03/99)	[3858-89-7]	$162
1118000	Chloroquine Phosphate (500 mg)	I			H (10/99)	[50-63-5]	$162
1121005	Chlorothiazide (200 mg)	H0B161			G (04/03)	[58-94-6]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1122008	Chlorotrianisene (1 g)	F				[569-57-3]	$162
1122700	Chloroxylenol (125 mg)	F2C259			F-1 (07/04) F (10/99)	[88-04-0]	$129
1122722	Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol)	G0C275			F-1 (07/04)	[5538-41-0]	$506
1123000	Chlorpheniramine Maleate (125 mg)	M0B020			L-1 (06/03)	[113-92-8]	$129
1123102	Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) (60 Tablets)	G0B259			F (06/03)	[113-92-8]	$162
1124003	Chlorphenoxamine Hydrochloride (200 mg)	F-1				[562-09-4]	$162
1125006	Chlorpromazine Hydrochloride (200 mg)	J			I (04/99)	[69-09-0]	$162
1126009	Chlorpropamide (200 mg)	H				[94-20-2]	$162
1127001	Chlorprothixene (200 mg)	F-1				[113-59-7]	$162
1129007	Chlortetracycline Hydrochloride (200 mg)	K0C185	1008 ug/mg (ai)		J-1 (12/04) J (02/02)	[64-72-2]	$162
1130006	Chlorthalidone (200 mg)	I0C255			H-1 (11/04) H (07/99)	[77-36-1]	$162
1119309	Chlorthalidone Related Compound A (15 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)	H0D251	1.00 mg/mg (ai)	2,3	G0C376 (09/05) F-3 (07/04)	n/f	$506
1130505	Chlorzoxazone (500 mg)	I			H (07/01)	[95-25-0]	$162
1130527	Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol)	G-1			G (11/00)	[95-85-2]	$506
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157			L (10/03) K (09/99)	[67-97-0]	$165
1131803	Delta-4,6-cholestadienol (30 mg)	F				[14214-69-8]	$506
1132001	Cholesteryl Caprylate (200 mg)	F				[1182-42-9]	$162
1133004	Cholestyramine Resin (500 mg)	I				[11041-12-6]	$129
1133503	Cholic Acid (2 g) (AS)	F3B159			F-2 (01/03)	[81-25-4]	$162
1133536	Choline Bitartrate (200 mg)	F0C057				[87-67-2]	$162
1133547	Choline Chloride (200 mg)	F0C058				[67-48-1]	$162
1133570	Chondroitin Sulfate Sodium (300 mg)	F0B256				[39455-18-0]	$162
1133638	Chromium Picolinate (100 mg)	F				[14639-25-9]	$162
1134007	Chymotrypsin (300 mg)	I			H (06/01)	[9004-07-3]	$162
1134030	Ciclopirox Olamine (125 mg)	H0C207			G (05/03)	[41621-49-2]	$129
1134051	Cilastatin Ammonium Salt (100 mg)	G0C334	945 ug/mg (ai)		F-1 (05/05) F (07/00)	n/f	$162
1134062	Cimetidine (200 mg)	I1C081			I (05/04)	[51481-61-9]	$162
1134073	Cimetidine Hydrochloride (200 mg)	F				[70059-30-2]	$162
1134109	Cinoxacin (200 mg)	F				[28657-80-9]	$162
1134313	Ciprofloxacin (125 mg)	G-1			G (05/01)	[85721-33-1]	$129
1134324	Ciprofloxacin Ethylenediamine Analog (25 mg)	J0A030			I (01/03) H-1 (02/99)	n/f	$506
1134335	Ciprofloxacin Hydrochloride (400 mg)	I0C265			H (02/05) G (04/00)	[86393-32-0]	$162
1134357	Cisplatin (100 mg)	H			G (03/01)	[15663-27-1]	$162
1134368	Citric Acid (200 mg)	F1B092			F-1 (01/04) F (07/02)	[77-92-9]	$162
1134379	Clarithromycin (75 mg)	F4B183			F-3 (01/04) F-2 (09/01)	[81103-11-9]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1134380	Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A)	G			F (04/01)	n/f	$506
1134404	Clavam-2-carboxylate Potassium (1 Pellet)	H0C089			G0B225 (12/03) F (10/03)	n/f	$506
1134426	Clavulanate Lithium (200 mg)	I1C270	0.952 mg/mg (ai)		I (02/05) H (09/02)	n/f	$162
1134506	Clemastine Fumarate (250 mg)	I			H (10/00)	[14976-57-9]	$162
1135000	Clidinium Bromide (2 g)	H0B115			G (03/05)	[3485-62-9]	$162
1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)	I				[76201-95-1]	$506
1136002	Clindamycin Hydrochloride (200 mg)	G4A017			G-3 (07/03) G-2 (05/99)	[58207-19-5]	$445
1137005	Clindamycin Palmitate Hydrochloride (200 mg)	F-2				[25507-04-4]	$445
1138008	Clindamycin Phosphate (125 mg)	I0C165			H-3 (04/04) H-2 (07/03) H-1 (02/99)	[24729-96-2]	$223
1138201	Clioquinol (500 mg)	M			L-1 (01/03)	[130-26-7]	$162
1138405	Clobetasol Propionate (200 mg)	F2C309	980 ug/mg (ai)		F-1 (03/05) F (10/01)	[25122-46-7]	$162
1138427	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	$506
1138507	Clocortolone Pivalate (200 mg)	G				[34097-16-0]	$162
1138904	Clofazimine (200 mg)	F				[2030-63-9]	$162
1139000	Clofibrate (1 g)	I			H (04/01)	[637-07-0]	$162
1140000	Clomiphene Citrate (500 mg)	H			G-1 (10/99)	[50-41-9]	$162
1140101	Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride)	F1B206			F (09/03)	n/f	$506
1140247	Clomipramine Hydrochloride (200 mg)	F0C075				[17321-77-6]	$162
1140305	Clonazepam **CIV** (200 mg)	G1B175			G (01/04) F-2 (01/00)	[1622-61-3]	$215
1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)	G2B110			G-1 (01/04) G (02/99)	n/f	$506
1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)	H			G (04/01)	[2011-66-7]	$506
1140349	Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide)	F0C340				n/f	$506
1140393	Clonidine (200 mg)	F0C401				[4205-90-7]	$162
1140407	Clonidine Hydrochloride (200 mg)	H0D106	1.000 mg/mg (dr)		G (05/05)	[4205-91-8]	$162
1140418	Clonidine Related Compound A (25 mg) (Acetylclonidine)	F0C373				[54707-71-0]	$506
1140429	Clonidine Related Compound B (25 mg) (2-[(E)-2,6-Dichlorophenylimino]-1-(1-{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)-imidazolidine)	F0C403	0.99 mg/mg (ai)			n/f	$506
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027			F-1 (06/03) F (12/99)	[57109-90-7]	$215
1140702	Clorsulon (200 mg)	F1B084			F (01/04)	[60200-06-8]	$162
1141002	Clotrimazole (200 mg)	K0C282			J (02/05) I (05/99)	[23593-75-1]	$129

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1141024	Clotrimazole Related Compound A (25 mg) ((o-chlorophenyl)diphenylmethanol)	I			H (10/01) G-1 (02/99)	[66774-02-5]	$506
1141909	Cloxacillin Benzathine (200 mg)	F-1			F (03/02)	[23736-58-5]	$162
1142005	Cloxacillin Sodium (200 mg)	L0B086			K (01/04)	[7081-44-9]	$162
1142107	Clozapine (100 mg)	F0C032				[5786-21-0]	$270
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074			H-2 (01/04) H-1 (02/99)	[53-21-4]	$215
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034			F-1 (11/02)	[3688-65-1]	$215
1144000	Codeine Phosphate **CII** (100 mg)	J0C200			I-1 (10/04) I (09/02) H-1 (01/00)	[41444-62-6]	$215
1145003	Codeine Sulfate **CII** (250 mg)	H-2			H-1 (01/02)	[6854-40-6]	$215
1146006	Colchicine (300 mg)	J			I (05/02)	[64-86-8]	$162
1146505	Colestipol Hydrochloride (200 mg)	F-1				[37296-80-3]	$162
1147009	Colistimethate Sodium (200 mg)	H1D234	0.420 mg/mg (dr)	2	H (09/05)	[8068-28-8]	$162
1148001	Colistin Sulfate (200 mg)	G-1			G (09/99)	[1264-72-8]	$162
1148500	Copovidone (100 mg)	F0C194				[2586-89-9]	$162
1148806	Corn Oil (1 g) (AS)	F0D181				[8001-30-7]	$162
1149004	Corticotropin (5.6 Units/vial; 5 vials)	M			L (06/99)	[9002-60-2]	$129
1150003	Cortisone Acetate (150 mg)	I				[50-04-4]	$162
1150207	Cottonseed Oil (1 g) (AS)	F0D173				[8001-29-4]	$162
1150353	Creatinine (100 mg)	F				[60-27-5]	$162
1150502	Cromolyn Sodium (500 mg)	J			I (06/00)	[15826-37-6]	$162
1150706	Crospovidone (200 mg)	G1C273			G (12/04)	[9003-39-8]	$162
1151006	Crotamiton (200 mg)	H-1			H (07/00)	[483-63-6]	$162
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N			M-3 (08/99)	[68-19-9]	$162
1152508	Cyclacillin (200 mg)	G				[3485-14-1]	$162
1152701	Cyclandelate (200 mg)	F0C384				[456-59-7]	$162
1154004	Cyclizine Hydrochloride (200 mg)				G (10/05)	[303-25-3]	$162
1154503	Cyclobenzaprine Hydrochloride (200 mg)	G0A013			F-3 (07/03)	[6202-23-9]	$162
1154558	Alpha Cyclodextrin (50 mg)	F-1			F (10/00)	[10016-20-3]	$162
1154569	Beta Cyclodextrin (250 mg)	G			F-1 (12/02)	[7585-39-9]	$162
1154707	Cyclomethicone 4 (200 mg)	F-2			F-1 (06/02)	[69430-24-6]	$162
1154809	Cyclomethicone 5 (200 mg)	G0D052			F-2 (07/05) F-1 (09/99)	[69430-24-6]	$162
1154900	Cyclomethicone 6 (200 mg)	F2B024			F-1 (03/03)	[69430-24-6]	$162
1156000	Cyclopentolate Hydrochloride (300 mg)	I0C424	0.999 mg/mg (dr)		H (03/05) G (04/00)	[5870-29-1]	$162
1157002	Cyclophosphamide (500 mg) (FOR U.S. SALE ONLY)	J1B200			J (02/05)	[6055-19-2]	$129
1157501	2-Cyclopropylmethylamino-5-chlorobenzophenone (50 mg)	F				n/f	$506
1158005	Cycloserine (200 mg)	G				[68-41-7]	$162
1158504	Cyclosporine (50 mg)	H-1			H (11/02) G-2 (03/00)	[59865-13-3]	$498
1158650	Cyclosporine Resolution Mixture (25 mg)	F				[108027-45-8] (U)	$428
1159008	Cyclothiazide (200 mg)	F-1				[2259-96-3]	$162
1161000	Cyproheptadine Hydrochloride (500 mg)	G			F-4 (11/02)	[41354-29-4]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1161509	L-Cysteine Hydrochloride (200 mg)	H			G (05/00)	[7048-04-6]	$162
1162002	Cytarabine (250 mg)	G-2			G-1 (07/00)	[147-94-4]	$162
1162308	Dacarbazine (125 mg)	H			G (01/99)	[4342-03-4]	$129
1162320	Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride)	H0C052			G (03/04) F (03/00)	[72-40-2]	$506
1162330	Dacarbazine Related Compound B (50 mg) (2-azahypoxanthine)	G0C325			F-1 (03/05) F (12/01)	[63907-29-9]	$624
1162400	Dactinomycin (50 mg)	I				[50-76-0]	$444
1162501	Danazol (200 mg)	H			G (10/00)	[17230-88-5]	$162
1164008	Dapsone (125 mg)	G-3			G-2 (08/99)	[80-08-0]	$129
1164700	Daunorubicin Hydrochloride (200 mg)	L0B307			K (11/03) J (08/00)	[23541-50-6]	$498
1165000	Decamethonium Bromide (250 mg)	F				[541-22-0]	$162
1166003	Deferoxamine Mesylate (500 mg)	I				[138-14-7]	$162
1166309	Dehydroacetic Acid (200 mg)	F				[520-45-6]	$162
1166400	Dehydrocarteolol Hydrochloride (100 mg)	F				n/f	$506
1166502	Dehydrocholic Acid (200 mg)	F-1			F (03/04)	[81-23-2]	$162
1169001	Demecarium Bromide (250 mg)	F				[56-94-0]	$162
1170000	Demeclocycline Hydrochloride (200 mg)	H1C036			H (08/04)G-1 (08/01)	[64-73-3]	$162
1171003	Denatonium Benzoate (200 mg)	I0B129			H (09/02)	[86398-53-0]	$162
1171706	Desacetyl Diltiazem Hydrochloride (50 mg)	J0C143	1.00 mg/mg (ai)		I (07/05) H (08/00)	[23515-45-9]	$506
1171900	Desflurane (0.5 mL)	F0C187				[57041-67-5]	$162
1171910	Desflurane Related Compound A (0.1 mL) (bis-(1,2,2,2-tetrafluoroethyl) ether)	F0C031				n/f	$506
1172006	Desipramine Hydrochloride (125 mg)	H-1			H (10/99)	[58-28-6]	$129
1173009	Deslanoside (100 mg)	H-1				[17598-65-1]	$162
1173235	Desogestrel (50 mg)	G0C390			F0B282 (11/04)	[54024-22-5]	$162
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	$506
1173257	Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel)	F0B284				n/f	$506
1173268	Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel)	F0B281				[54048-10-1]	$506
1173508	Desoximetasone (200 mg)	H0B036			G (01/04)	[382-67-2]	$162
1174001	Desoxycorticosterone Acetate (200 mg)	J0C014			I (01/04) H (05/00)	[56-47-3]	$162
1175004	Desoxycorticosterone Pivalate (125 mg)	H0C276			G (01/04)	[808-48-0]	$129
1176007	Dexamethasone (125 mg)	J				[50-02-2]	$129
1176506	Dexamethasone Acetate (200 mg)	G			F-1 (06/99)	[1177-87-3]	$162
1177000	Dexamethasone Phosphate (200 mg)	J1B070			J (08/03) I (03/00)	[312-93-6]	$162
1178002	Dexbrompheniramine Maleate (200 mg)	J			I (03/03)	[2391-03-9]	$162
1179005	Dexchlorpheniramine Maleate (500 mg)	G1A025			G (12/02)	[2438-32-6]	$162
1179504	Dexpanthenol (500 mg)	J0C293			I (08/04) H (02/02)	[81-13-0]	$166
1179708	Dextran 40 (50 mg)	F0C247				[9004-54-0]	$162
1179741	Dextran 70 (50 mg)	F0C260				[9004-54-0]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1179854	Dextran 4 Calibration (100 mg)	F0C002				[9004-54-0]	$162
1179865	Dextran 10 Calibration (100 mg)	F0C010				[9004-54-0]	$162
1179876	Dextran 40 Calibration (100 mg)	F0C011				[9004-54-0]	$162
1179720	Dextran 40 System Suitability (200 mg)	F0B181				[9004-54-0]	$162
1179887	Dextran 70 Calibration (100 mg)	F0C013				[9004-54-0]	$162
1179763	Dextran 70 System Suitability (200 mg)	F0B182				[9004-54-0]	$162
1179898	Dextran 250 Calibration (100 mg)	F0C039				[9004-54-0]	$162
1179650	Dextran T-10 (200 mg)	F0D238	1.000 mg/mg (dr)	1		[9004-54-0]	$162
1179800	Dextran Vo Marker (100 mg)	F0B242				[9004-54-0]	$162
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	1.000 mg/mg (dr)		H (05/05) G (08/03) F-6 (12/99)	[51-63-8]	$225
1180503	Dextromethorphan (2 g)	H			G (06/00)	[125-71-3]	$506
1181007	Dextromethorphan Hydrobromide (500 mg)	J0B167			I (07/03)	[6700-34-1]	$162
1181302	Dextrose (500 mg)	J-1			J (11/02) I (08/99)	[50-99-7]	$129
1181506	Diacetylated Monoglycerides (200 mg)	G				[68990-54-5]	$162
1182000	Diacetylfluorescein (200 mg)	H			G (01/02)	[596-09-8]	$162
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J			I-1 (10/99)	[1502-95-0]	$215
1184005	Diatrizoic Acid (100 mg)	G				[50978-11-5]	$162
1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)	I			H (02/00)	[1713-07-1]	$506
1185008	Diazepam **CIV** (100 mg)	I			H (12/01)	[439-14-5]	$215
1185020	Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone)	I			H-1 (11/02) H (04/00)	[1022-13-5]	$506
1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)	I1C102			I (12/04) H (04/01)	[5220-02-0]	$506
1186000	Diazoxide (200 mg)	G1C017			G (12/03)	[364-98-7]	$162
1187003	Dibucaine Hydrochloride (200 mg)	I			H-2 (01/03)	[61-12-1]	$162
1187080	Dibutyl Phthalate (200 mg)	F0D125				[84-74-2]	$162
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	99.2% (ai)	1		[109-43-3]	$162
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010				[480-30-8]	$215
1188006	Dichlorphenamide (200 mg)	G-1				[120-97-8]	$162
1188800	Diclofenac Sodium (200 mg)	H0B150			G-1 (03/04) G (05/01)	[15307-79-6]	$162
1188811	Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl)indolin-2-one)	H			G (05/02)	[15362-40-0]	$510
1189009	Dicloxacillin Sodium (500 mg)	J0C182			I0B142 (09/04) H (05/03)	[13412-64-1]	$162
1190008	Dicumarol (200 mg)	G				[66-76-2]	$162
1191000	Dicyclomine Hydrochloride (125 mg)	H			G (03/99)	[67-92-5]	$129
1192003	Dienestrol (125 mg)	I				[84-17-3]	$129
1193006	Diethylcarbamazine Citrate (200 mg)	G-1				[1642-54-2]	$162
1193301	Diethylene Glycol Monoethyl Ether (0.5 mL/ampule)	F0B095				[111-90-0]	$162
1193505	Diethyl Phthalate (200 mg)	G			F-1 (03/00)	[84-66-2]	$162
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H				[134-80-5]	$215
1195001	Diethylstilbestrol (200 mg)	K5B291			K-4 (05/04)	[56-53-1]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1197007	Diethyltoluamide (3 g)	H				[134-62-3]	$129
1197302	Diflorasone Diacetate (200 mg)	G			F-1 (03/00)	[33564-31-7]	$162
1197506	Diflunisal (200 mg)	G				[22494-42-4]	$162
1198000	Digitalis (3 g)	F				[8031-42-3]	$162
1199002	Digitoxin (200 mg)	M				[71-63-6]	$162
1200000	Digoxin (250 mg)	O0B096			N-1 (04/03)	[20830-75-5]	$162
1200600	Dihydrocapsaicin (25 mg)	G0C071			F-1 (12/03) F (01/00)	[19408-84-5]	$270
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	0.997 mg/mg (dr)	2	H (09/05) G (03/01)	[5965-13-9]	$215
1201002	17alpha-Dihydroequilin (50 mg)	I0C277			H (07/04)	[6639-99-2]	$216
1202005	Dihydroergotamine Mesylate (250 mg) **(List Chemical)**	J0B085			I (03/03)	[6190-39-2]	$162
1203008	Dihydrostreptomycin Sulfate (200 mg)	J				[5490-27-7]	$162
1204000	Dihydrotachysterol (30 mg/ampule; 4 ampules)	J0D250	0.996 mg/mg (ai)	2	I (06/05)	[67-96-9]	$162
1204102	Dihydroxyacetone (250 mg)	F				[96-26-4]	$162
1204805	Diloxanide Furoate (200 mg)	F0C026				[3736-81-0]	$162
1205003	Diltiazem Hydrochloride (200 mg)	I				[33286-22-5]	$162
1206006	Dimenhydrinate (100 mg)	J0B055			I (06/03)	[523-87-5]	$162
1208001	Dimethisoquin Hydrochloride (2 g)	G				[2773-92-4]	$162
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F				[41992-23-8]	$162
1211006	Dimethyl Sulfoxide (3 g)	G0C198			F-3 (07/04) F-2 (05/02)	[67-68-5]	$216
1213001	Dinoprost Tromethamine (50 mg)	F				[38562-01-5]	$1,586
1213103	Dinoprostone (50 mg)	F0C030				[363-24-6]	$1,586
1214004	Dioxybenzone (150 mg)	F1B277			F (10/03)	[131-53-3]	$162
1216000	Diphemanil Methylsulfate (500 mg)	H				[62-97-5]	$162
1217909	Diphenhydramine Citrate (125 mg)	H0B128			G (04/03)	[88637-37-0]	$129
1218005	Diphenhydramine Hydrochloride (200 mg)	J0B013			I (07/03)	[147-24-0]	$162
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I			H (03/02)	[3810-80-8]	$215
1220302	Dipivefrin Hydrochloride (200 mg)	I			H (06/99)	[64019-93-8]	$162
1220506	Dipyridamole (200 mg)	H			G-1 (01/99)	[58-32-2]	$162
1220700	Dirithromycin (200 mg)	F				[62013-04-1]	$162
1221000	Disodium Guanylate (300 mg) (FCC)	F-1				[5550-12-9]	$162
1222002	Disodium Inosinate (500 mg) (FCC)	F				[4691-65-0]	$162
1222501	Disopyramide Phosphate (200 mg)	H-1			H (03/02)	[22059-60-5]	$162
1223005	2,4-Disulfamyl-5-trifluoromethylaniline (125 mg)	G				[654-62-6]	$506
1224008	Disulfiram (200 mg)	F-3			F-2 (07/02)	[97-77-8]	$162
1224507	Dobutamine Hydrochloride (600 mg)	H-1			H (01/00)	[49745-95-1]	$162
1224700	Docusate Calcium (500 mg)	H0B044			G-1 (07/02)	[128-49-4]	$162
1224802	Docusate Sodium (500 mg)	K0D134	0.988mg/mg (an)	2	J (09/05) I-1 (05/02)	[577-11-7]	$162
1224904	Docusate Potassium (100 mg)	F-1			F (11/99)	[7491-09-0]	$162
1224959	Dolasetron Mesylate (200 mg)	F0C319				[115956-13-3]	$162
1224960	Dolasetron Mesylate Related Compound A (25 mg) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride)	F0C321				n/f	$506
1225204	Dopamine Hydrochloride (200 mg)	G			F-5 (05/02)	[62-31-7]	$162
1225281	Dorzolamide Hydrochloride (500 mg)	F0C040				[130693-82-2]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
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				n/f	$506
1225000	Doxapram Hydrochloride (200 mg)	F4C053			F-3 (07/04)	[7081-53-0]	$162
1225419	Doxazosin Mesylate (200 mg)	F0C079				[77883-43-3]	$162
1225500	Doxepin Hydrochloride (500 mg)	I				[1229-29-4]	$162
1225703	Doxorubicin Hydrochloride (50 mg)	K			J (06/02)	[25316-40-9]	$498
1226003	Doxycycline Hyclate (200 mg)	I			H (01/00)	[24390-14-5]	$162
1227006	Doxylamine Succinate (300 mg)	I0B266			H (01/04)	[562-10-7]	$162
1229001	Droperidol (250 mg)	I0C029			H-1 (01/05) H (04/99)	[548-73-2]	$162
1230000	Dyclonine Hydrochloride (200 mg)	G				[536-43-6]	$162
1231003	Dydrogesterone (200 mg)	I0B114			H (01/04)	[152-62-5]	$162
1231502	Dyphylline (200 mg)	G-2			G-1 (11/02)	[479-18-5]	$162
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018				[90028-20-9]	$541
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019				[84696-11-7]	$541
1231808	Econazole Nitrate (200 mg)	G1C346	1.00 mg/mg (ai)		G (07/05)	[68797-31-9]	$162
1232006	Edetate Calcium Disodium (200 mg)	H0B272			G-3 (11/04) G-2 (11/99)	[23411-34-9]	$162
1233009	Edetate Disodium (200 mg)	H			G-2 (04/02)	[6381-92-6]	$162
1233508	Edetic Acid (200 mg)	F-1				[60-00-4]	$162
1234001	Edrophonium Chloride (200 mg)	H			G (08/99)	[116-38-1]	$162
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291				[84696-12-5]	$541
1234806	Emedastine Difumarate (100 mg)	F0C059				[87233-62-3]	$162
1235004	Emetine Hydrochloride (300 mg)	H0B201			G (05/03)	[316-42-7]	$162
1235274	Enalaprilat (300 mg)	J0C268			I (11/04) H (03/01) G (08/99)	[84680-54-6]	$129
1235300	Enalapril Maleate (200 mg)	J1C267	0.992 mg/mg (ai)		J (05/05) I (06/01)	[76095-16-4]	$162
1235503	Endotoxin (10,000 USP Endotoxin Units)	G2B274			G-1 (12/03) G (06/99)	n/f	$162
1235809	Enflurane (1 mL)	G-1			G (02/01)	[13838-16-9]	$162
1236007	Ephedrine Sulfate (200 mg) **(List Chemical)**	H-2			H-1 (11/02)	[134-72-5]	$162
1236506	4-Epianhydrotetracycline Hydrochloride (50 mg)	J0C041			I-1 (12/03) I (06/00)	[4465-65-0]	$506
1236801	Epilactose (200 mg)	G			F-1 (06/00)	[50468-56-9]	$506
1237000	Epinephrine Bitartrate (200 mg)	O				[51-42-3]	$162
1237509	Epitetracycline Hydrochloride (200 mg)	F				[23313-80-6]	$506
1238002	Equilin (25 mg)	I1B290			I (11/04) H-1 (05/00)	[474-86-2]	$216
1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275			O (02/04) N (12/99)	[50-14-6]	$175
1239504	Ergoloid Mesylates (300 mg)	I			H-1 (01/00)	[8067-24-1]	$162
1240004	Ergonovine Maleate (100 mg) **(List Chemical)**	N			M-1 (07/02)	[129-51-1]	$162
1241007	Ergosterol (50 mg)	H				[57-87-4]	$162
1241506	Ergotamine Tartrate (150 mg) **(List Chemical)**	I0B174			H (01/04)	[379-79-3]	$162
1241550	Ergotaminine (100 mg) **(List Chemical)**	G0B177			F-1 (06/04)	[639-81-6]	$162
1242000	Erythromycin (250 mg)	M			L (08/99)	[114-07-8]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1242010	Erythromycin B (150 mg)	G1C080			G (11/04) F-1 (09/01) F (05/01)	[527-75-3]	$162
1242021	Erythromycin C (50 mg)	F-3			F-2 (01/03) F-1 (02/02) F (02/99)	n/f	$506
1242032	Erythromycin Related Compound N (50 mg) (N-Demethylerythromycin A)	F2A023			F-1 (06/04) F (09/99)	n/f	$506
1243002	Erythromycin Estolate (200 mg)	H			G (01/03)	[3521-62-8]	$162
1245008	Erythromycin Ethylsuccinate (200 mg)	H			G-1 (06/01)	[1264-62-6]	$162
1246000	Erythromycin Gluceptate (200 mg)	H			G (07/03)	[23067-13-2]	$162
1247003	Erythromycin Lactobionate (200 mg)	H-1			H (01/02)	[3847-29-8]	$162
1248006	Erythromycin Stearate (200 mg)	H0B187			G-1 (05/03)	[643-22-1]	$162
1249009	Erythrosine Sodium (100 mg)	F				[49746-10-3]	$162
1250008	Estradiol (500 mg)	L0C337	0.996 mg/mg (an)		K1B007 (07/05) K (04/03)	[50-28-2]	$162
1251000	Estradiol Benzoate (250 mg) (AS)	G-1				[50-50-0]	$162
1252003	Estradiol Cypionate (200 mg)	G-1			G (02/00)	[313-06-4]	$162
1254009	Estradiol Valerate (100 mg)	L			K (05/02)	[979-32-8]	$162
1254508	Estriol (100 mg)	J			I-1 (06/01)	[50-27-1]	$162
1255001	Estrone (200 mg)	K1B099			K (07/03) J-1 (07/00)	[53-16-7]	$162
1255500	Estropipate (500 mg)	J0B262			I (12/03) H (09/01)	[7280-37-7]	$162
1256004	Ethacrynic Acid (200 mg)	F				[58-54-8]	$162
1257007	Ethambutol Hydrochloride (200 mg)	H			G (08/02)	[1070-11-7]	$162
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011				[113-18-8]	$215
1260001	Ethinyl Estradiol (150 mg)	Q0C162			P1B193 (11/04) P0B052 (01/04) P (03/03) O (08/99)	[57-63-6]	$162
1260012	Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol)	F0B252				n/f	$506
1261004	Ethionamide (200 mg)	H0B148			G (03/03)	[536-33-4]	$162
1262801	Ethopabate (125 mg)	F				[59-06-3]	$162
1262823	Ethopabate Related Compound A (25 mg) (Methyl-4-acetamido-2-hydroxybenzoate)	F				n/f	$506
1263000	Ethopropazine Hydrochloride (300 mg)	G				[1094-08-2]	$162
1264002	Ethosuximide (125 mg)	H			G-2 (11/01) G-1 (05/99)	[77-67-8]	$129
1264501	Ethotoin (200 mg)	F				[86-35-1]	$162
1265005	Ethoxzolamide (200 mg)	F				[452-35-7]	$162
1265504	Ethylcellulose (1 g)	H-1			H (06/99)	[9004-57-3]	$162
1266008	Ethyl Maltol (1 g) (FCC)	H				[4940-11-8]	$162
1266507	Ethylnorepinephrine Hydrochloride (200 mg)	F				[3198-07-0]	$162
1267000	Ethylparaben (200 mg)	I0A016			H (01/04)	[120-47-8]	$162
1267500	Ethyl Vanillin (200 mg)	F2B134			F-1 (04/04)	[121-32-4]	$162
1268003	Ethynodiol Diacetate (200 mg)	I0A033			H-1 (01/03) H (04/01)	[297-76-7]	$162
1268502	Etidronate Disodium (200 mg)	G			F-2 (02/03)	[7414-83-7]	$162
1268604	Etidronic Acid Monohydrate (1 g)	G			F-1 (05/99)	[2809-21-4]	$162
1268706	Etodolac (400 mg)	G			F (10/01)	[41340-25-4]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1268728	Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-b]-indole-1-acetic acid)	F-1			F (05/02)	[109518-50-5]	$506
1268808	Etoposide (300 mg)	H0C315			G (11/04)	[33419-42-0]	$129
1268852	Etoposide Resolution Mixture (30 mg)	F0B209				[33419-42-0]	$506
1269200	Famotidine (125 mg)	H-1			H (11/02) G (03/99)	[76824-35-6]	$129
1269389	Felodipine (200 mg)	G0D065	0.999 mg/mg (ai)		F-1 (04/05) F (09/02)	[72509-76-3]	$162
1269390	Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate)	F0B207				[96302-71-7]	$506
1269403	Fenbendazole (100 mg)	F				[43210-67-9]	$506
1269414	Fenbendazole Related Compound A (30 mg) (Methyl (1H-benzimidazole-2-yl)carbamate)	F0D009	0.99 mg/mg (ai)			[10605-21-7]	$506
1269425	Fenbendazole Related Compound B (30 mg) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate)	F0D008	0.99 mg/mg (ai)			n/f	$506
1269458	Fenoldopam Mesylate (200 mg)	F0C125				[67227-57-0]	$162
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				n/f	$506
1269470	Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate)	F0C126				n/f	$506
1269505	Fenoprofen Calcium (500 mg)	G-1				[53746-45-5]	$162
1269550	Fenoprofen Sodium (500 mg)	G			F-1 (05/02)	[66424-46-2]	$162
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	101.0% (ai)			[7782-63-0]	$162
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264			J2B227 (11/04) J-1 (09/03) J (05/02) I (06/00)	[990-73-8]	$250
1270377	Fexofenadine Hydrochloride (200 mg)	F0D244	0.996 mg/mg (ai)	1		[138452-21-8]	$162
1270388	Fexofenadine Related Compound A (25 mg) (4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid)	F0D245	0.99 mg/mg (ai)	1		n/f	$506
1270399	Fexofenadine Related Compound B (25 mg) (3-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid hydrochloride)	F0D246		1		n/f	$506
1270402	Finasteride (200 mg)	F				[98319-26-7]	$162
1270800	Flecainide Acetate (200 mg)	F2A022			F-1 (02/05) F (06/03)	[54143-56-5]	$162
1270821	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	$506
1271008	Floxuridine (250 mg)	F-2			F-1 (08/01)	[50-91-9]	$162
1271700	Fluconazole (200 mg)	F0D262	1.00 mg/mg (ai)	1		[86386-73-4]	$162
1271711	Fluconazole Related Compound A (10 mg) (2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D080	0.95 mg/mg (ai)	1		n/f	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1271722	Fluconazole Related Compound B (10 mg) (2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D081	0.92 mg/mg (ai)	1		[81886-51-3]	$506
1272000	Flucytosine (200 mg)	F				[2022-85-7]	$162
1272204	Fludarabine Phosphate (300 mg)	F0C374				[75607-67-9]	$162
1273003	Fludrocortisone Acetate (250 mg)	H			G (08/01)	[514-36-3]	$162
1273808	Flumazenil (200 mg)	F0C305				[78755-81-4]	$811
1274006	Flumethasone Pivalate (200 mg)	I			H (01/02)	[2002-29-1]	$162
1274505	Flunisolide (200 mg)	I			H (01/01)	[77326-96-6]	$162
1274607	Flunixin Meglumine (300 mg)	G			F-1 (04/02) F (09/99)	[42461-84-7]	$162
1275009	Fluocinolone Acetonide (100 mg)	J			I (11/99)	[67-73-2]	$162
1276001	Fluocinonide (100 mg)	I				[356-12-7]	$162
1277004	Fluorescein (200 mg)	G0B171			F-1 (02/03)	[2321-07-5]	$162
1277252	Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz)	J0C294			I (08/04) H (04/99)	n/f	$476
1277274	Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz)	G0D270		2	F (06/05)	n/f	$506
1277300	Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz)	G				n/f	$506
1277354	Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz)	G				n/f	$506
1277401	Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica (5.25 oz)	G-1			G (08/99)	n/f	$506
1277423	Fluoride Dentifrice: Sodium Monofluorophosphate (1500 ppm)/Silica (5.25 oz)	F-1			F (07/99)	n/f	$506
1277456	Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz)	H0B105			G (11/02)	n/f	$506
1278007	Fluorometholone (200 mg)	I0B184			H-1 (11/02)	[426-13-1]	$162
1278109	Fluorometholone Acetate (200 mg)	F				[3801-06-7]	$162
1278302	Fluoroquinolonic Acid (50 mg)	H0C140			G (01/05) F-1 (12/99)	[86393-33-1]	$506
1279000	Fluorouracil (250 mg)	H2D190	1.000 mg/mg (dr)	2	H-1 (09/05) H (01/02)	[51-21-8]	$162
1279804	Fluoxetine Hydrochloride (200 mg)	F2C132			F-1 (02/05) F (11/99)	[59333-67-4]	$162
1279815	Fluoxetine Related Compound A (15 mg) (N-methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride)	H0C131			G (06/04) F-1 (05/01) F (06/00)	n/f	$506
1279826	Fluoxetine Related Compound B (5 mL of a 0.01N HCl solution, approx. 2 mg/mL) (N-methyl-3-phenylpropylamine)	G0D023	approx. 2 mg/mL (ai)		F3C085 (05/05) F-2 (06/04) F-1 (09/02) F (09/00)	[23580-89-4]	$506
1279837	Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid)	F0C352				n/f	$506
1280009	Fluoxymesterone **CIII** (200 mg)	G-2			G-1 (04/00)	[76-43-7]	$215
1280803	Fluphenazine Decanoate Dihydrochloride (500 mg)	G			F-1 (10/01)	n/f	$165
1281001	Fluphenazine Enanthate Dihydrochloride (125 mg)	H			G (02/99)	[3105-68-8]	$129
1282004	Fluphenazine Hydrochloride (125 mg)	H				[146-56-5]	$129
1284000	Flurandrenolide (100 mg)	I0B245			H (09/03)	[1524-88-5]	$162

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	0.996 mg/mg (ai)		I (09/03)	[1172-18-5]	$215
1285308	Flurazepam Related Compound C (50 mg) (5-chloro-2-(2-diethylaminoethyl(amino)-2'-fluorobenzophenone Hydrochloride)	H-1				n/f	$506
1285603	Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one)	I0C092			H (01/04)	[2886-65-9]	$506
1285750	Flurbiprofen (200 mg)	G				[5104-49-4]	$162
1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)	H			G (03/01)	n/f	$506
1285807	Flurbiprofen Sodium (200 mg)	F				[56767-76-1]	$162
1285851	Flutamide (200 mg)	H0B278			G (11/04) F-1 (06/00)	[13311-84-7]	$162
1285862	o-Flutamide (50 mg)	F-1			F (01/00)	n/f	$506
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P			O (07/00)	[59-30-3]	$162
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176			H-1 (04/04) H (01/00)	[1492-18-8]	$162
1286060	Formononetin (50 mg)	F0C196				[485-72-3]	$541
1286300	10-Formylfolic Acid (25 mg)	F2B226			F-1 (01/04)	[134-05-4]	$506
1286366	Fosphenytoin Sodium (250 mg)	F0C156				[92134-98-0]	$162
1286504	Fructose (125 mg)	I-2			I-1 (11/02) I (08/99)	[57-48-7]	$129
1286708	Fumaric Acid (200 mg)	G-1			G (04/02)	[110-17-8]	$162
1286800	Furazolidone (200 mg)	G-2			G-1 (01/01)	[67-45-8]	$162
1287008	Furosemide (125 mg)	J1B131			J (10/03)	[54-31-9]	$129
1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)	J			I (08/02)	n/f	$506
1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)	I0C248			H (08/04) G-3 (03/01)	[3086-91-7]	$506
1287303	Gabapentin (250 mg)	F				[60142-96-3]	$162
1287325	Gabapentin Related Compound A (100 mg) (3,3-pentamethylene-5-butyrolactam)				F (10/05)	[64744-50-9]	$506
1287507	Gadodiamide (500 mg)	F				[131410-48-5]	$162
1287518	Gadodiamide Related Compound A (50 mg) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide)	F				n/f	$506
1287529	Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid)	F				n/f	$506
1287609	Gadopentetate Monomeglumine (500 mg)	F				[92923-57-4]	$162
1287631	Gadoteridol (500 mg)	F				[120066-54-8]	$162
1287642	Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid)	F0A002				[120041-08-9]	$506
1287653	Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt)	F0B198				[112188-16-6]	$506
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]	$506
1287675	Gadoversetamide (200 mg)	F0C172				[131069-91-5]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1287686	Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium)	F0C173				n/f	$506
1287700	Galactose (200 mg)	F-4			F-3 (05/01)	[59-23-4]	$506
1288000	Gallamine Triethiodide (200 mg)	F				[65-29-2]	$162
1288306	Ganciclovir (200 mg)	F0C287				[82410-32-0]	$379
1288317	Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one)	F0C288				n/f	$649
1288463	Gemcitabine Hydrochloride (200 mg)	F0D037	0.997 mg/mg (ai)			[122111-03-9]	$162
1288500	Gemfibrozil (200 mg)	H				[25812-30-0]	$162
1288510	Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid)				F0C101 (10/05)	n/f	$506
1289003	Gentamicin Sulfate (200 mg)				L0C279 (08/04) K (12/04) J-1 (04/00)	[1405-41-0]	$162
1290002	Gentian Violet (650 mg)	F				[548-62-9]	$162
1291005	Gibberellic Acid (200 mg) (FCC)	G			F (04/01)	[77-06-5]	$162
1291504	Powdered Ginger (500 mg)	F				n/f	$270
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289				[50647-08-0]	$541
1292008	Gitoxin (50 mg)	G			F-3 (07/00)	[4562-36-1]	$506
1292507	Glipizide (125 mg)	G1C174			G (07/04)	[29094-61-9]	$129
1292609	Glipizide Related Compound A (25 mg) (N-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide)	G-1			G (04/99)	n/f	$506
1294003	Glucagon (25 mg, 0.95 U/mg) **DISCONTINUED**				H (01/05)	[16941-32-5]	$162
1294207	Glucosamine Hydrochloride (200 mg)	F0C363				[66-84-2]	$162
1294976	Glutamic Acid (200 mg)	F0C069				[56-86-0]	$162
1294808	Glutamine (100 mg)	F0B244				[56-85-9]	$162
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F				n/f	$702
1295006	Glutethimide **CII** (500 mg)	F				[77-21-4]	$215
1295505	Glyburide (200 mg)	G			F-2 (11/02)	[10238-21-8]	$162
1295607	Glycerin (2 mL)	H0C073			G1A001 (04/04) G (12/02) F (04/99)	[56-81-5]	$162
1295709	Glyceryl Behenate (200 mg)	F3B113			F-2 (03/03)	[18641-57-1]	$162
1295800	Glycine (200 mg)	F-3			F-2 (02/00)	[56-40-6]	$162
1296009	Glycopyrrolate (200 mg)	H0B304			G (05/04)	[596-51-0]	$162
1295888	Glycyrrhizic Acid (25 mg)	F0C006				[1405-86-3]	$506
1297001	Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package)	H			G (07/00)	[9002-61-3]	$1,040
1298004	Gramicidin (200 mg)	I			H-1 (07/02)	[1405-97-6]	$162
1299007	Griseofulvin (200 mg)	I			H-1 (09/02)	[126-07-8]	$162
1299200	Griseofulvin Permeability Diameter (2 g)	J0C380			I0C138 (10/04) H (08/03)	[126-07-8]	$162
1300004	Guaiacol (1 g)	K			J (04/00)	[90-05-1]	$162
1301007	Guaifenesin (200 mg)	I			H (09/02)	[93-14-1]	$162
1301404	Guanabenz Acetate (200 mg)	G			F-1 (06/00)	[23256-50-0]	$162
1301608	Guanadrel Sulfate (200 mg)	F-1				[22195-34-2]	$162
1301801	Guanethidine Monosulfate (200 mg)	F				[645-43-2]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1302000	Guanethidine Sulfate (500 mg)	G-1				[60-02-6]	$162
1302101	Guanfacine Hydrochloride (125 mg)	G0B123			F-1 (02/03) F (11/99)	[29110-48-3]	$129
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224			F (12/04)	[23092-17-3]	$215
1302509	Halcinonide (300 mg)	F				[3093-35-4]	$162
1303002	Haloperidol (200 mg)	I			H-1 (05/02)	[52-86-8]	$162
1303013	Haloperidol Related Compound A (15 mg) (4,4'-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone)	K0C362			J (12/04)	[67987-08-0]	$506
1303308	Haloprogin (200 mg)	F				[777-11-7]	$162
1303501	Halothane (1 mL)	G0D068			F-1 (03/05)	[151-67-7]	$162
1304005	Heparin Sodium (10 x 1 mL)	K-5			K-4 (08/03) K-3 (02/99)	[9041-08-1]	$162
1305008	Hexachlorophene (500 mg)	I			H-2 (01/01)	[70-30-4]	$162
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	1.00 mg/mg (ai)			[82240-09-3]	$562
1307003	Hexobarbital **CIII** (500 mg)	F				[56-29-1]	$215
1308006	Hexylcaine Hydrochloride (1 g)	F-1				[532-76-3]	$162
1308200	Hexylene Glycol (125 mg)	G			F-2 (04/02) F-1 (04/99)	[107-41-5]	$162
1308307	Hexylresorcinol (200 mg)	F				[136-77-6]	$162
1308505	L-Histidine (200 mg)	G0A018			F-2 (01/03) F-1 (04/00)	[71-00-1]	$162
1309009	Histamine Dihydrochloride (250 mg)	M0C280			L (07/04)	[56-92-8]	$162
1310008	Homatropine Hydrobromide (200 mg)	H2C049			H-1(02/05) H (08/02)	[51-56-9]	$162
1311000	Homatropine Methylbromide (250 mg)	J			I-1 (06/01)	[80-49-9]	$162
1311306	Homopolymer Polypropylene (3 Strips)	F0C096				[9003-07-0]	$162
1311408	Homosalate (500 mg)	G0D072	0.995 mg/mg (ai)		F0B102 (04/05)	[118-56-9]	$162
1312003	Hyaluronidase (500 mg)				H (06/05)	[9001-54-1]	$162
1313006	Hydralazine Hydrochloride (200 mg)	K			J-1 (09/02)	[304-20-1]	$162
1314009	Hydrochlorothiazide (200 mg)	I			H (05/02)	[58-93-5]	$162
1315001	Hydrocodone Bitartrate **CII** (250 mg)	K0C217			J0A026 (01/05) I-1 (12/02) I (07/02) H-2 (11/99)	[34195-34-1]	$215
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214				[847-86-9]	$534
1316004	Hydrocortisone (200 mg)	M1C110			M (10/04) L (09/00)	[50-23-7]	$162
1317007	Hydrocortisone Acetate (200 mg)	K			J (10/99)	[50-03-3]	$162
1317302	Hydrocortisone Butyrate (200 mg)	H				[13609-67-1]	$162
1318000	Hydrocortisone Cypionate (200 mg)	F				[508-99-6]	$162
1319002	Hydrocortisone Hemisuccinate (200 mg)	H			G-3 (03/02) G-2 (08/99)	[83784-20-7]	$162
1320001	Hydrocortisone Phosphate Triethylamine (200 mg)	F-1				n/f	$162
1321004	Hydrocortisone Valerate (200 mg)	F-1			F (07/02)	[57524-89-7]	$162
1322007	Hydroflumethiazide (200 mg)	F-2				[135-09-1]	$162
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372			I (01/05) H-2 (03/01)	[71-68-1]	$215

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1324002	Hydroquinone (500 mg)	H0C249			G-1 (10/04) G (11/01) F-4 (02/99)	[123-31-9]	$162
1325005	Hydroxyamphetamine Hydrobromide (200 mg)	G			F (06/01)	[306-21-8]	$162
1327000	Hydroxychloroquine Sulfate (200 mg)	J0B297			I (05/04)	[747-36-4]	$162
1329006	Hydroxyprogesterone Caproate (200 mg)	H				[630-56-8]	$162
1329709	Hydroxypropyl Betadex (200 mg)	F0B295				[128446-35-5]	$162
1329800	Hydroxypropyl Cellulose (200 mg)	F-1				[9004-64-2]	$162
1332000	Hydroxyurea (200 mg)	H			G (01/00)	[127-07-1]	$162
1333003	Hydroxyzine Hydrochloride (500 mg)	I0C385	0.998 mg/mg (dr)		H (05/05)	[2192-20-3]	$162
1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)	H				[303-26-4]	$506
1334006	Hydroxyzine Pamoate (500 mg)	H0C016			G-1 (07/03)	[10246-75-0]	$162
1335009	Hyoscyamine Sulfate (125 mg)	H0C193			G2A007 (09/04) G-1 (08/02) G (10/99)	[6835-16-1]	$129
1335202	Hyperoside (50 mg)	F				[482-36-0]	$889
1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)	H0C387			G-1 (11/04) G (02/02)	[9004-65-3]	$162
1335279	Hypromellose Acetate Succinate (100 mg)	F0D275		1		[71138-97-1]	$162
1335304	Hypromellose Phthalate (100 mg)	F-1			F (12/00)	[9050-31-1]	$162
1335508	Ibuprofen (750 mg)	J			I (06/02)	[15687-27-1]	$162
1335701	Idarubicin Hydrochloride (50 mg)	H0C061			G (11/03) F (06/00)	[57852-57-0]	$498
1336001	Idoxuridine (250 mg)	H1B230			H (07/04)	[54-42-2]	$162
1336205	Ifosfamide (500 mg)	G			F-1 (11/00) F (02/99)	[3778-73-2]	$162
1336500	Imidazole (200 mg)	G1B132			G (01/04)	[288-32-4]	$506
1336806	Imidurea (200 mg)	H			G (10/99)	[39236-46-9]	$162
1337004	Iminodibenzyl (25 mg)	I0C253			H (11/04)	[494-19-9]	$506
1337809	Imipenem Monohydrate (100 mg)	G1C296	930 ug/mg (ai)		G (01/05) F (01/01)	[74431-23-5]	$162
1338007	Imipramine Hydrochloride (200 mg)	I			H (09/01)	[113-52-0]	$162
1338801	Indapamide (250 mg)	H			G (07/02)	[26807-65-8]	$162
1339000	Indigotindisulfonate Sodium (500 mg)	H1B153			H (06/03)	[860-22-0]	$162
1340009	Indocyanine Green (200 mg)	I0B045			H (09/01)	[3599-32-4]	$162
1341001	Indomethacin (200 mg)	J0B165			I (01/04) H (05/99)	[53-86-1]	$162
1342004	Insulin (100 mg)	H				[9004-10-8]	$162
1342106	Insulin Human (100 mg)	I0C383	26.6 USP Insulin Human Units/mg (ai)		H1A031 (07/05) H (11/02) G (04/00)	[11061-68-0]	$162
1342208	Insulin (Beef) (100 mg)	F				[11070-73-8]	$162
1342300	Insulin (Pork) (100 mg)	F				[12584-58-6]	$162
1342503	Iocetamic Acid (200 mg)	F				[16034-77-8]	$162
1343007	Iodipamide (200 mg)	G				[606-17-7]	$162
1343517	Iodixanol (200 mg)	F0B240				[92339-11-2]	$162
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	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
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]	$506
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	$506
1344305	o-Iodohippuric Acid (100 mg)	F				[147-58-0]	$162
1344509	Iodoquinol (100 mg)	H			G (07/02)	[83-73-8]	$162
1344600	Iohexol (100 mg)	F-1			F (01/99)	[66108-95-0]	$129
1344622	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	$506
1344644	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]	$506
1344666	Iohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide)	F-1			F (09/03)	n/f	$506
1344702	Iopamidol (200 mg)	G				[60166-93-0]	$162
1344724	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]	$506
1344735	Iopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide)	F				n/f	$506
1344804	Iopromide (400 mg)	F				[73334-07-3]	$162
1344826	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	$506
1344837	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	$506
1345002	Iothalamic Acid (200 mg)	G				[2276-90-6]	$162
1345104	Ioversol (200 mg)	F				[87771-40-2]	$162
1345115	Ioversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)	F				[76801-93-9]	$506
1345126	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	$506
1345159	Ioxaglic Acid (100 mg)	F				[59017-64-0]	$162
1345206	Ioxilan (400 mg)	F				[107793-72-6]	$162
1345228	Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2-hydroxyethyl)carbamoyl benzoic acid)	F				[22871-58-5]	$506
1346005	Ipodate Calcium (200 mg)	F				[1151-11-7]	$162
1347008	Ipodate Sodium (200 mg)	F-1				[1221-56-3]	$162
1347755	Isoamyl Methoxycinnamate (750 mg/ampule)	F0B017				[71617-10-2]	$162
1348000	Isocarboxazid (200 mg)	F-1				[59-63-2]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1348500	Isoetharine Hydrochloride (250 mg)	F-2				[2576-92-3]	$162
1348907	Isoflupredone Acetate (200 mg)	F0C109				[338-98-7]	$162
1349003	Isoflurane (1 mL)	H1C199			H (12/04)	[26675-46-7]	$162
1349014	Isoflurane Related Compound A (0.1 mL) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether)	F0C232				n/f	$506
1349025	Isoflurane Related Compound B (0.1 mL) (2,2,2-Trifluoroethyldifluoromethyl ether)	F0C233				n/f	$506
1349502	L-Isoleucine (200 mg)	F-2			F-1 (09/02)	[73-32-5]	$162
1349604	Isomalathion (50 mg)	F1B107			F (01/03)	[3344-12-5]	$506
1349659	Isometheptene Mucate (200 mg)	F				[7492-31-1]	$162
1349706	Isoniazid (200 mg)	H				[54-85-3]	$162
1350002	Isopropamide Iodide (200 mg)	F-2				[71-81-8]	$162
1350400	Isopropyl Myristate (500 mg)	I1C183			I (01/05)	[110-27-0]	$162
1350603	Isopropyl Palmitate (500 mg)	I			H (10/99)	[142-91-6]	$162
1351005	Isoproterenol Hydrochloride (125 mg)	K				[51-30-9]	$129
1352008	Isosorbide (75% solution, 1 g)	I			H-2 (10/00)	[652-67-5]	$162
1353000	Diluted Isosorbide Dinitrate (500 mg of 25% mixture with mannitol)	I-1			I (10/99)	[87-33-2]	$162
1353500	Isotretinoin (200 mg)	I			H (10/00)	[4759-48-2]	$162
1354003	Isoxsuprine Hydrochloride (200 mg)	F-3				[579-56-6]	$162
1354207	Isradipine (200 mg)	G0B054			F (05/03)	[75695-93-1]	$162
1354218	Isradipine Related Compound A (25 mg) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate)	F				n/f	$506
1354309	Ivermectin (200 mg)	F0B196				[70288-86-7]	$162
1355006	Kanamycin Sulfate (200 mg)	J			I (06/99)	[25389-94-0]	$162
1355709	Powdered Kava Extract (1 g)	F0C161				n/f	$270
1355753	Kawain (200 mg)	F0C160				[500-64-1]	$216
1356009	Ketamine Hydrochloride **CIII** (250 mg)	G-2			G-1 (07/00)	[1867-66-9]	$215
1356020	Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol)	F0C118				[6740-87-0]	$506
1356508	Ketoconazole (200 mg)	G4B179			G-3 (01/04) G-2 (06/01) G-1 (01/99)	[65277-42-1]	$162
1356632	Ketoprofen (200 mg)	H0B216			G (07/04) F-2 (05/99)	[22071-15-4]	$162
1356643	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid)	G				[107257-20-5]	$506
1356665	Ketorolac Tromethamine (200 mg)	G			F-2 (04/99)	[74103-07-4]	$162
1356654	Labetalol Hydrochloride (200 mg)	G			F-2 (01/02) F-1 (03/01)	[32780-64-6]	$162
1356698	Lactase (200 mg)	F0D032	105,000 USP units/g (ai)			[9031-11-2]	$162
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	88.5% (ai)	1		[50-21-5]	$162
1356676	Anhydrous Lactose (100 mg)	G1C004			G (12/04) F (06/01)	[63-42-3]	$162
1356687	Lactitol (500 mg)	F0B005				[81025-04-9]	$162
1356701	Lactose Monohydrate (500 mg)	H0C151			G-1 (07/05) G (08/02)	[5989-81-1]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1356803	Lactulose (1 g)	H			G-1 (08/00)	[4618-18-2]	$162
1356836	Lamivudine (200 mg)	F0C361				[134678-17-4]	$162
1356847	Lamivudine Resolution Mixture A (10 mg)	F0D024				[134678-17-4]	$506
1356880	Lanolin (20 g)	F				[8006-54-0]	$162
1356905	Lanolin Alcohols (5 g)	F				[8027-33-6]	$162
1356916	Lansoprazole (200 mg)				F0B310 (10/05)	[103577-45-3]	$162
1356927	Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]-methyl]sulfonyl]benzimidazole)	F0B311				n/f	$506
1356950	Lauroyl Polyoxylglycerides (500 mg) (AS)	F0D020				n/f	$162
1356971	Letrozole (200 mg)	F0B170				[112809-51-5]	$162
1356982	Letrozole Related Compound A (15 mg) (4,4'-(1H-1,3,4-triazol-1-ylmethylene)dibenzonitrile)				F0B168 (10/05)	n/f	$506
1357001	L-Leucine (200 mg)	H0B237			G-1 (04/04) G (08/00)	[61-90-5]	$162
1358004	Leucovorin Calcium (500 mg)	J2B219			J-1 (07/04) J (05/02)	[1492-18-8]	$166
1358503	Leuprolide Acetate (200 mg)	F0C430	0.907 mg/mg (an,fb)			[74381-53-6]	$1,586
1359302	Levamisole Hydrochloride (125 mg)	F2C122			F-1 (05/04)	[16595-80-5]	$129
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	98% (ai)		F(08/05)	[33817-09-3]	$215
1359801	Levobunolol Hydrochloride (200 mg)	G				[27912-14-7]	$162
1359903	Levocarnitine (400 mg)	G0B197			F-2 (06/03) F-1 (12/00)	[541-15-1]	$162
1359925	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]	$506
1361009	Levodopa (200 mg)	I			H (09/00)	[59-92-7]	$162
1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)	K			J (01/03) I (06/00)	[27244-64-0]	$506
1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)	I0C300			H (07/04)		$506
1362500	Levonordefrin (200 mg)	F-1				[829-74-3]	$162
1363004	Levopropoxyphene Napsylate (300 mg)	G				[55557-30-7]	$162
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	1.000 mg/mg (an)		H (07/05) G (03/01)	[5985-38-6]	$215
1365000	Levothyroxine (500 mg)	K			J (10/00)	[51-48-9]	$162
1366002	Lidocaine (250 mg)	L				[137-58-6]	$162
1367005	Lincomycin Hydrochloride (200 mg)	H2B130			H-1 (01/04)	[7179-49-9]	$162
1367504	Lindane (200 mg)	F-2				[58-89-9]	$162
1367708	Linoleoyl Polyoxylglycerides (100 mg)	F0C283				n/f	$162
1368008	Liothyronine (250 mg)	L1C262			L (08/04) K (08/01)	[6893-02-3]	$162
1368609	Lisinopril (300 mg)	I1C045			I (11/04) H (09/01) G (10/99)	[83915-83-7]	$162
1369000	Lithium Carbonate (300 mg)	G0B031			F-2 (01/03) F-1 (01/01)	[554-13-2]	$162
1370000	Loperamide Hydrochloride (200 mg)	H0C202			G-2 (09/04) G-1 (02/03)	[34552-83-5]	$162
1370203	Loracarbef (200 mg)	F				[121961-22-6]	$162
1370225	Loracarbef L-Isomer (25 mg)	F				n/f	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1370270	Loratadine (200 mg)	F0C414				[79794-75-5]	$270
1370280	Loratadine Related Compound A (15 mg) (8-Chloro-6,11-dihydro-11(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b] pyridine)	F0D229				[100643-71-8]	$506
1370291	Loratadine Related Compound B (15 mg) (8-Chloro-6,11-dihydro-11(N-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine)	F0D230				n/f	$506
1370305	Lorazepam **CIV** (200 mg)	I0C048			H0B023 (06/04)	[846-49-1]	$215
1370327	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]	$506
1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)	G			F-2 (01/04)	[2958-36-3]	$506
1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)	H			G (01/03) F-3 (01/02)	n/f	$506
1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)	G0A014			F-2 (01/04)	[54643-79-7]	$506
1370360	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	$506
1370462	Losartan Potassium (250 mg)	F0D287	0.998 mg/mg (ai)	1		[124750-99-8]	$162
1370600	Lovastatin (125 mg)	H2C012			H1B067 (01/04) H (08/03)	[75330-75-5]	$129
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]]-)	G0C326			F0B235 (09/04)	n/f	$506
1370702	Loxapine Succinate (125 mg)	G0B026			F-2 (06/03) F-1 (07/01) F (03/99)	[27833-64-3]	$129
1370906	Lynestrenol (20 mg)	F0B314				[52-76-6]	$211
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I				[50-37-3]	$562
1371501	L-Lysine Acetate (200 mg)	F1C027			F (11/04)	[57282-49-2]	$162
1372005	L-Lysine Hydrochloride (200 mg)	H			G (07/00)	[657-27-2]	$162
1373008	Mafenide Acetate (400 mg)	F1D216	0.999 mg/mg (an)	3	F (07/05)	[13009-99-9]	$162
1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)	G0C351	1.00 mg/mg (dr)		F (08/05)	n/f	$506
1374000	Magaldrate (200 mg)	F-1				[74978-16-8]	$162
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	41.8% MgO (ai)	1		[546-93-0]	$162
1374248	Magnesium Chloride (1 g) (AS)	F0D157	100.3% (ai)			[7791-18-6}	$162
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	98.5% (dr)			[1309-42-8]	$162
1374306	Magnesium Salicylate (200 mg)	F2B081			F-1 (01/04)	[18917-95-8]	$162
1374340	Magnesium Stearate (5 g) (AS)	F0D214	65% Stearate 29% Palmitate 4.8% Mg (ai)	1		[577-04-0]	$162
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	99.8% (ig)			[10034-99-8]	$162
1374408	Malathion (500 mg)	F-1			F (08/01)	[121-75-5]	$162
1374500	Maleic Acid (300 mg)	G			F-2 (12/00)	[110-16-7]	$506

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1374601	Malic Acid (200 mg)	G0B158			F-1 (04/03)	[617-48-1]	$162
1374907	Maltitol (200 mg)	G			F-1 (12/99)	[585-88-6]	$162
1375003	Maltol (4 g) (FCC)	G			F-1 (12/99)	[118-71-8]	$162
1375058	Mandelic Acid (500 mg)	F				[90-64-2]	$162
1375069	Mangafodipir Trisodium (200 mg)	F0D272	0.996 mg/mg (an)	1		[140678-14-4]	$162
1375070	Mangafodipir Related Compound A (15 mg) (manganese (II) dipyridoxyl monophosphate sodium salt)	F0D266		1		n/f	$506
1375080	Mangafodipir Related Compound B (15 mg) (manganese (II) dipyridoxyl diphosphate mono-overalkylated sodium salt)	F0D267		1		n/f	$506
1375127	Manganese Chloride (1 g) (AS)	F0D150	99.6% (dr)			[13446-34-9]	$162
1375149	Manganese Sulfate (1 g) (AS)	F0D151	99.8% (ai)			[10034-96-5]	$162
1375105	Mannitol (200 mg)	I0B212			H (03/04)	[69-65-8]	$162
1375207	Maprotiline Hydrochloride (200 mg)	H			G (07/02)	[10347-81-6]	$162
1375309	Mazindol **CIV** (350 mg)	H			G (02/03)	[22232-71-9]	$215
1375502	Mebendazole (200 mg)	G1C195			G (11/04)	[31431-39-7]	$162
1375706	Mebrofenin (100 mg)	F				[78266-06-5]	$162
1376006	Mecamylamine Hydrochloride (200 mg)	F-2				[826-39-1]	$162
1376505	Mechlorethamine Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	F-1			F (09/00)	[55-86-7]	$162
1377009	Meclizine Hydrochloride (500 mg)	I-1				[31884-77-2]	$162
1377508	Meclocycline Sulfosalicylate (300 mg)	G				[73816-42-9]	$162
1377803	Meclofenamate Sodium (500 mg)	H				[6385-02-0]	$162
1378001	Medroxyprogesterone Acetate (200 mg)	I0D013	0.995 mg/mg (ai)	2	H-2 (09/05) H-1 (04/03)	[71-58-9]	$162
1378012	Medroxyprogesterone Acetate Related Compound A (25 mg) (4,5-beta-Dihydromedroxyprogesterone acetate)	F0C427	1.00 mg/mg (ai)			n/f	$520
1379004	Medrysone (500 mg)	F				[2668-66-8]	$162
1379605	Mefenamic Acid (200 mg)	G0C025			F3A032 (08/04) F-2 (01/03)	[61-68-7]	$162
1379106	Megestrol Acetate (500 mg)	I			H (05/00)	[595-33-5]	$162
1379300	Melphalan Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	H0B296	0.975 mg/mg (ai)		G (01/05)	[3223-07-2]	$162
	Melting Point Standards - See Cross Reference Section						
1381006	Menadione (200 mg) (Vitamin K3)	H-3			H-2 (02/00)	[58-27-5]	$162
1381709	Menthol (250 mg)	I0B049			H (04/03)	[2216-51-5]	$162
1381742	Menthyl Anthranilate (500 mg/ampule)	F0B103				[134-09-8]	$162
1382009	Mepenzolate Bromide (200 mg)	F				[76-90-4]	$162
1383001	Meperidine Hydrochloride **CII** (200 mg)	I			H-1 (12/99)	[50-13-5]	$215
1384004	Mephentermine Sulfate (250 mg) **DISCONTINUED**			9	F-1 (04/05)	[1212-72-2]	$162
1385007	Mephenytoin (250 mg)	G				[50-12-4]	$162
1386000	Mephobarbital **CIV** (250 mg)	G			F (01/01)	[115-38-8]	$215
1387002	Mepivacaine Hydrochloride (200 mg)	H			G-4 (02/99)	[1722-62-9]	$162
1388005	Meprednisone (200 mg)	G				[1247-42-3]	$162
1389008	Meprobamate **CIV** (200 mg)	G-1			G (03/02)	[57-53-4]	$215
1390007	Meprylcaine Hydrochloride (200 mg)	F				[956-03-6]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1391000	3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt (75 mg)	G				n/f	$506
1392002	Mercaptopurine (500 mg)	I2C263			I-1 (10/04) I (07/02) H (12/99)	[6112-76-1]	$162
1392454	Meropenem (300 mg)	F0C201				[119478-56-7]	$189
1392705	Mesalamine (200 mg)	H0C341			G1B001 (06/05) G (01/03) F-1 (03/00)	[89-57-6]	$162
1393005	Mesoridazine Besylate (250 mg)	J0C117			I-1 (12/04)	[32672-69-8]	$162
1394008	Mestranol (200 mg)	K0C065			J (07/04) I-1 (09/99)	[72-33-3]	$162
1395500	Metaproterenol Sulfate (200 mg)	F-3				[5874-97-5]	$162
1396003	Metaraminol Bitartrate (200 mg)	F-3				[33402-03-8]	$162
1396309	Metformin Hydrochloride (200 mg)	G0D271	0.999 mg/mg (ai)	2	F0C209 (08/05)	[1115-70-4]	$189
1396310	Metformin Related Compound A (50 mg) (1-Cyanoguanidine)	F0C210				[461-58-5]	$506
1396400	Methacrylic Acid Copolymer Type A (200 mg)	G0B140			F-2 (04/03)	n/f	$162
1396502	Methacrylic Acid Copolymer Type B (200 mg)	G0B141			F-2 (04/03)	n/f	$162
1396604	Methacrylic Acid Copolymer Type C (100 mg)	G1B088			G (08/03)	n/f	$129
1397006	Methacycline Hydrochloride (200 mg)	I0C348	903 ug/mg (ai)	2	H (10/05) G (04/01)	[3963-95-9]	$162
1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163			H-1 (08/03)	[1095-90-5]	$215
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I				[51-57-0]	$215
1401001	Methantheline Bromide (200 mg)	F-1				[53-46-3]	$162
1402004	Methapyrilene Fumarate (200 mg)	F-1				[33032-12-1]	$162
1404000	Methaqualone **CI** (500 mg)	F-1				[72-44-6]	$215
1405002	Metharbital **CIII** (200 mg)	F-2			F-1 (07/99)	[50-11-3]	$215
1406005	Methazolamide (500 mg)	H0B239			G-1 (05/04)	[554-57-4]	$162
1407008	Methdilazine (200 mg)	F-1				[1982-37-2]	$162
1408000	Methdilazine Hydrochloride (200 mg)	G				[1229-35-2]	$162
1409003	Methenamine (500 mg)	H0C047			G (05/04)	[100-97-0]	$162
1409502	Methenamine Hippurate (200 mg)	F				[5714-73-8]	$162
1409604	Methenamine Mandelate (200 mg)	G0C304			F-2 (01/05) F-1 (11/00)	[587-23-5]	$162
1410002	Methicillin Sodium (500 mg) (AS)	J0C333			I1B186 (11/04) I (03/03) H (03/00)	[7246-14-2]	$162
1411005	Methimazole (200 mg)	G			F (02/01)	[60-56-0]	$162
1411504	L-Methionine (200 mg)	G			F-2 (11/99)	[63-68-3]	$162
1412008	Methocarbamol (200 mg)	H2B029			H-1 (03/04)	[532-03-6]	$162
1413000	Methohexital **CIV** (500 mg)	G0D252	1.000 mg/mg (an)		F-2 (08/05)	[18652-93-2]	$215
1414003	Methotrexate (500 mg)	I				[59-05-2]	$162
1415006	Methotrimeprazine (125 mg)	F-2			F-1 (05/99)	[60-99-1]	$129
1416009	Methoxamine Hydrochloride (200 mg)	F				[61-16-5]	$162
1417001	Methoxsalen (500 mg)	H				[298-81-7]	$162
1418004	Methoxyflurane (1 mL)	G				[76-38-0]	$162
1419007	Methoxyphenamine Hydrochloride (250 mg)	F				[5588-10-3]	$162
1421009	Methscopolamine Bromide (200 mg)	G1D004	0.999 mg/mg (dr)		G (02/05)	[155-41-9]	$162
1422001	Methsuximide (500 mg)	F-2			F-1 (08/99)	[77-41-8]	$162
1424007	Methyclothiazide (200 mg)	G				[135-07-9]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1424018	Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)	G			F-2 (12/00)	n/f	$506
1424222	Methyl Benzylidene Camphor (200 mg)	F0B118				[36861-47-9]	$162
1424233	Methyl Caprate (300 mg)	F				[110-42-9]	$162
1424244	Methyl Caproate (300 mg)	F				[106-70-7]	$162
1424255	Methyl Caprylate (300 mg)	G0D064	1.00 mg/mg (ai)		F (07/05)	[111-11-5]	$162
1424506	Methylcellulose (1 g) (AS)	G0B222			F-2 (05/03)	[9004-67-5]	$162
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F				[15589-00-1]	$215
1426002	Methyldopa (500 mg)	I				[41372-08-1]	$162
1427005	Methyldopate Hydrochloride (200 mg)	G-2				[2508-79-4]	$162
1428008	Methylene Blue (250 mg)	H0D163	1.000 mg/mg (dr) (Colorimetric) 0.90 mg/mg (dr) (TLC)		G (08/05)	[7220-79-3]	$162
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1				[6292-91-7]	$215
1430000	Methylergonovine Maleate (50 mg) **(List Chemical)**	J			I (05/02)	[57432-61-8]	$162
1430305	Methyl Laurate (500 mg)	G0C356	0.998 mg/mg (ai)		F (03/05)	[111-82-0]	$162
1430327	Methyl Linoleate (5 x 50 mg)	F				[112-63-0]	$162
1430349	Methyl Linolenate (5 x 50 mg)	F				[301-00-8]	$162
1430509	3-O-Methylmethyldopa (50 mg)	G-1				n/f	$506
1431002	Methyl 5-methyl-3-isoxazolecarboxylate (25 mg)	F-1			F (01/01)	n/f	$506
1431501	Methyl Myristate (300 mg)	G0C357	0.998 mg/mg (ai)		F (03/05)	[124-10-7]	$162
1431556	Methyl Oleate (500 mg)	G0C148			F (04/04)	[112-62-9]	$162
1431603	Methyl Palmitate (300 mg)	F				[112-39-0]	$162
1431625	Methyl Palmitoleate (300 mg)	F				n/f	$162
1432005	Methylparaben (125 mg)	J-1			J (03/03))	[99-76-3]	$129
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241			I (04/05) H (05/01)	[298-59-9]	$172
1434000	Methylphenidate Hydrochloride Erythro Isomer **CII** (25 mg) **DISCONTINUED**; please order 1434011				J0B294 (04/05) I0A006 (09/03) H-1 (01/03) H (06/01)	[298-59-9]	$582
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	0.5 mg/mL (ai)			n/f	$582
1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)	G			F-2 (10/99)	n/f	$506
1435003	Methylprednisolone (200 mg)	H				[83-43-2]	$162
1436006	Methylprednisolone Acetate (200 mg)	H0D148	0.995 mg/mg (ai)		G-2 (05/05) G-1 (02/00)	[53-36-1]	$162
1437009	Methylprednisolone Hemisuccinate (200 mg)	I0C146			H (07/04)	[2921-57-5]	$162
1437508	Methyl Stearate (300 mg)	F				[112-61-8]	$162
1438001	Methyltestosterone **CIII** (200 mg)	J			I (11/01)	[58-18-4]	$215
1440003	Methysergide Maleate (200 mg)	H				[129-49-7]	$162
1440808	Metoclopramide Hydrochloride (500 mg)	H0D121	0.999 mg/mg (an)		G (06/05) F-2 (06/99)	[54143-57-6]	$162
1441006	Metocurine Iodide (300 mg)	G				[7601-55-0]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1441200	Metolazone (200 mg)	G0B246			F-1 (05/03)	[17560-51-9]	$162
1441287	Metoprolol Fumarate (200 mg)	F				[119637-66-0]	$162
1441232	Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol)	F0C343				n/f	$541
1441243	Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane)	F0C377				n/f	$541
1441254	Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]-benzaldehyde)	F0C344				n/f	$541
1441265	Metoprolol Related Compound D (50 mg) ((+/-)N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine)	F0C378				n/f	$541
1441298	Metoprolol Succinate (200 mg)	F0C415	0.998 mg/mg (ai)			[98418-47-4]	$162
1441301	Metoprolol Tartrate (200 mg)	H1B059			H (01/04) G-1 (11/99)	[56392-17-7]	$162
1441505	Metrizamide (500 mg)	F				[31112-62-6]	$162
1442009	Metronidazole (100 mg)	J0C316	1.000 mg/mg (dr)		I (07/05)	[443-48-1]	$162
1443001	Metyrapone (200 mg)	H			G (06/01)	[54-36-4]	$162
1443205	Metyrosine (200 mg)	F				[672-87-7]	$162
1443250	Mexiletine Hydrochloride (200 mg)	F-2			F-1 (09/02)	[5370-01-4]	$162
1443307	Mezlocillin Sodium (350 mg)	G				[59798-30-0]	$162
1443409	Miconazole (200 mg)	G-1			G (07/02)	[22916-47-8]	$162
1443500	Miconazole Nitrate (200 mg)	J0D011	0.997 mg/mg (dr)		I (06/06) H (06/99)	[22832-87-7]	$162
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321				[84604-20-6]	$270
1443908	Milrinone (500 mg)				F0C050 (09/05)	[78415-72-2]	$270
1443919	Milrinone Related Compound A (50 mg) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide)	F0C051				[80047-24-1]	$506
1444004	Minocycline Hydrochloride (200 mg)	I0C178			H-3 (04/04) H-2 (07/02)	[13614-98-7]	$162
1444208	Minoxidil (125 mg)	H1C168			H (03/04) G (05/99)	[38304-91-5]	$129
1444279	Mirtazapine (350 mg)	F0D155	0.999 mg/mg (an)			[61337-67-5]	$832
1444707	Mitomycin (50 mg)	K			J (07/01)	[50-07-7]	$498
1445007	Mitotane (500 mg)	G0C044			F (07/04)	[53-19-0]	$162
1445200	Mitoxantrone Hydrochloride (400 mg)	I0D174	0.990 mg/mg (an)		H (05/05) G (03/01)	[70476-82-3]	$518
1445211	Mitoxantrone System Suitability Mixture (0.3 mg)	F0D010				n/f	$520
1445459	Molindone Hydrochloride (500 mg)	F				[15622-65-8]	$162
1445470	Mometasone Furoate (200 mg)	G0B073			F-1 (04/03) F (02/01)	[83919-23-7]	$162
1445481	Monensin Sodium (200 mg)	F0B293				[22373-78-0]	$162
1445506	Monobenzone (200 mg)	F				[103-16-2]	$162
1445801	Mono- and Di-acetylated Monoglycerides (200 mg)	F				[68990-54-5]	$162
1446000	Monoglycerides (125 mg)	H				[68990-53-4]	$129
1446804	Monostearyl Maleate (100 mg)	G			F-2 (04/00)	[2424-62-6]	$506
1446950	Moricizine Hydrochloride (250 mg)	F1D057	0.999 mg/mg (an)		F (03/05)	[29560-58-5]	$406
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G				[6009-81-0]	$215

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1448005	Morphine Sulfate **CII** (500 mg)	M0D016	0.999 mg/mg (an)		L0B056 (04/05) K (06/03) J-1 (07/00)	[6211-15-0]	$345
1448504	Moxalactam Disodium (500 mg)	F-1				[64953-12-4]	$162
1448901	Mupirocin (50 mg)	F2C158			F-1 (12/04) F (03/02)	[12650-69-0]	$162
1448923	Mupirocin Lithium (100 mg)	H0C176	926 ug/mg (ai)		G (03/05) F (02/01)	[73346-79-9]	$162
1449008	Myristyl Alcohol (1 g)	G			F (02/02)	[112-72-1]	$162
1449518	Nabumetone (200 mg)	F0C072				[42924-53-8]	$162
1449530	Nabumetone Related Compound A (15 mg) (1-(6-Methoxy-2-naphthyl)-but-1-en-3-one)	F0D165				n/f	$506
1449700	Nadolol (200 mg)	G0C308	0.995 mg/mg (ai)		F-3 (04/05) F-2 (04/02)	[42200-33-9]	$162
1450007	Nafcillin Sodium (200 mg)	H				[7177-50-6]	$162
1450404	Naftifine Hydrochloride (200 mg)	F				[65473-14-5]	$162
1451000	Nalidixic Acid (200 mg)	G				[389-08-2]	$162
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I				[57-29-4]	$215
1453005	Naloxone (125 mg)	L0B124			K-1 (12/02) K (07/01)	[465-65-6]	$129
1453504	Naltrexone (200 mg)	H0C150			G1B039 (03/04) G (02/03)	[16590-41-3]	$162
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride)	F				n/f	$506
1454008	Nandrolone **CIII** (50 mg)	F4D144	1.00 mg/mg (ai)		F-3 (04/05)	[434-22-0]	$582
1455000	Nandrolone Decanoate **CIII** (250 mg)	I				[360-70-3]	$215
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H				[62-90-8]	$215
1457006	Naphazoline Hydrochloride (200 mg)	K				[550-99-2]	$162
1457301	Naproxen (200 mg)	I-1			I (03/03) H-1 (01/01)	[22204-53-1]	$162
1457403	Naproxen Sodium (200 mg)	J0C379	0.999 mg/mg (dr)		I (07/05)	[26159-34-2]	$162
1457469	Naratriptan Hydrochloride (125 mg)	F0C360	0.998 mg/mg (ai)			[143388-64-1]	$216
1457505	Natamycin (200 mg)	J0D180	0.917 mg/mg (ai)		I (06/05) H (11/99)	[7681-93-8]	$162
1458009	Neomycin Sulfate (200 mg)	L-2			L-1 (09/01) L (02/99)	[1405-10-3]	$162
1459001	Neostigmine Bromide (200 mg)	G				[114-80-7]	$162
1460000	Neostigmine Methylsulfate (200 mg)	I			H (07/00)	[51-60-5]	$162
1460500	Netilmicin Sulfate (500 mg)	I0C388	653 ug/mg (dr)		H (01/05) G (05/02)	[56391-57-2]	$162
1460703	Nevirapine Anhydrous (100 mg)	F0D159	0.997 mg/mg (ai)			[129618-40-2]	$162
1460714	Nevirapine Hemihydrate (100 mg)	F0D034				n/f	$162
1460725	Nevirapine Related Compound A (15 mg) (5,11-Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2-b2',3'-e][1,4]diazepin-6-one)	F0D035				n/f	$506
1460736	Nevirapine Related Compound B (15 mg) (5,11-Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one)	F0D033				n/f	$506
1461003	Niacin (200 mg)	H2C121			H-1 (01/05)	[59-67-6]	$162
1462006	Niacinamide (500 mg) (Vitamin B3)	M-1			M (02/01)	[98-92-0]	$162
1463304	Nicotine Bitartrate Dihydrate (500 mg)	G1C070			G (05/05) F (05/99)	[6019-06-3]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1463508	Nifedipine (125 mg)	J0B243			I-1 (04/04)	[21829-25-4]	$129
1463600	Nifedipine Nitrophenylpyridine Analog (25 mg)	K			J (04/01)	n/f	$506
1463701	Nifedipine Nitrosophenylpyridine Analog (25 mg)	K			J (07/02)	n/f	$506
1464001	Nitrofurantoin (500 mg)	J			I-1 (11/02)	[67-20-9]	$162
1465004	Nitrofurazone (200 mg)	H-1			H (09/01)	[59-87-0]	$162
1465503	Nitrofurfural Diacetate (100 mg)	G0D066	0.99 mg/mg (ai)		F-1 (12/04)	[92-55-7]	$506
1466007	Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine)	H0B100			G (07/03)	n/f	$506
1466506	Diluted Nitroglycerin (5 ampules, approx. 200 mg of a 0.948% solution in propylene glycol each)	G				[55-63-0]	$162
1467804	Nizatidine (200 mg)	G			F-1 (06/00)	[76963-41-2]	$162
1467950	Nonoxynol 9 (0.5 mL)	H-1			H (03/02)	[26027-38-3]	$162
1468002	Nonoxynol 10 (200 mg)	F				[26027-38-3]	$162
1468400	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]	$582
1468501	Norepinephrine Bitartrate (125 mg)	I0C381			H (04/05)	[69815-49-2]	$129
1469005	Norethindrone (200 mg)	K0C307	0.998 mg/mg (ai)	2	J1B065 (09/05) J-1 (05/03) J (07/02) I-1 (03/01)	[68-22-4]	$162
1470004	Norethindrone Acetate (100 mg)	J0B072			I (04/03) H (06/99)	[51-98-9]	$162
1471007	Norethynodrel (200 mg)	G				[68-23-5]	$162
1471506	Norfloxacin (200 mg)	H			G (04/01)	[70458-96-7]	$162
1471914	Norgestimate (200 mg)	F0C086				[35189-28-7]	$162
1472000	Norgestrel (125 mg)	J0C269			I (07/04) H (05/99)	[6533-00-2]	$129
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177			H (11/04)	n/f	$582
1474005	Nortriptyline Hydrochloride (200 mg)	I1D054	1.000 mg/mg (dr)		I (05/05) H (04/00)	[894-71-3]	$162
1474504	Noscapine (500 mg)	G				[128-62-1]	$162
1475008	Novobiocin (200 mg)				G-2 (05/05)	[303-81-1]	$162
1476000	Nylidrin Hydrochloride (200 mg)	F-2				[849-55-8]	$162
1477003	Nystatin (200 mg)	O0D177	5751 Nystatin units/mg (dr)	2	N1B004 (09/05) N (01/03)	[1400-61-9]	$162
1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)				G0C024 (09/05) F0B032 (12/03)	[5466-77-3]	$162
1477411	Octocrylene (500 mg)	G0C211			F0B104 (05/04)	[6197-30-4]	$162
1477502	Octoxynol 9 (200 mg)	G			F-2 (07/00)	[9002-93-1]	$162
1477808	Octyldodecanol (200 mg)	G			F-1 (07/99)	[5333-42-6]	$162
1477943	Octyl Salicylate (400 mg)	F0B091				[118-60-5]	$162
1478108	Ofloxacin (200 mg)	F-2			F-1 (08/02)	[82419-36-1]	$162
1478152	Oleoyl Polyoxylglycerides (100 mg)	F0C313				n/f	$162
1478254	Olive Oil (1 g) (AS)	F0D175		1		[8001-25-0]	$162
1478505	Omeprazole (200 mg)	H1B211			H (05/04) G-1 (04/02) G (09/01)	[73590-58-6]	$162
1478582	Ondansetron Hydrochloride (300 mg)	G0D154	0.993 mg/mg (an)		F0C222 (05/05)	[103639-04-9]	$216

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1478593	Ondansetron Related Compound A (50 mg) (3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride)	F0C191				[119812-29-2]	$506
1478618	Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one)	F0C251				[27397-31-1]	$506
1478629	Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one)	F0C226				n/f	$506
1478630	Ondansetron Resolution Mixture (50 mg)	F0D242				n/f	$506
1479009	Orphenadrine Citrate (200 mg)	G			F-4 (05/02)	[4682-36-4]	$162
1481000	Oxacillin Sodium (200 mg)	J			I (03/02)	[7240-38-2]	$162
1481500	Oxamniquine (200 mg) **DISCONTINUED**			9	F (10/05)	[21738-42-1]	$162
1481703	Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) **DISCONTINUED**			9	F (10/05)	n/f	$506
1481805	Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) **DISCONTINUED**			9	F (10/05)	n/f	$506
1482003	Oxandrolone **CIII** (50 mg)	G0B220			F-4 (07/03)	[53-39-4]	$215
1482207	Oxaprozin (200 mg)	F0C115				[21256-18-8]	$162
1483006	Oxazepam **CIV** (200 mg)	H0D259	1.000 mg/mg (dr)		G-1 (08/05) G (12/00)	[604-75-1]	$215
1483301	Oxfendazole (200 mg)	F0C128				[53716-50-0]	$162
1483505	Oxprenolol Hydrochloride (200 mg)	I0C344			H (02/05)	[6452-73-9]	$162
1484009	Oxtriphylline (500 mg)	G				[4499-40-5]	$162
1485001	Oxybenzone (150 mg)	H0B263			G (11/03) F-2 (12/99)	[131-57-7]	$162
1485103	Oxybutynin Chloride (200 mg)	G-1			G (11/02)	[1508-65-2]	$162
1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)	G			F-2 (01/00)	[4335-77-7]	$506
1485125	Oxybutynin Related Compound B (20 mg) (Cyclohexyl mandelic acid methyl ester)	F0D061				[10399-13-0]	$506
1485136	Oxybutynin Related Compound C (20 mg) (4-(Ethylmethylamino)but-2-ynyl(+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride)	F0D062				n/f	$506
1485191	Oxycodone **CII** (200 mg)	I1D206	0.990 mg/mg (dr)		I0B046 (08/05) H (01/03) G-1 (01/01)	[76-42-6]	$215
1486004	Oxymetazoline Hydrochloride (200 mg)	J0C206			I (03/05)	[2315-02-8]	$162
1487007	Oxymetholone **CIII** (200 mg)	G1B247			G (10/03)	[434-07-1]	$215
1488000	Oxymorphone **CII** (500 mg)	H0B214			G (03/03)	[76-41-5]	$215
1489002	Oxyphenbutazone (1 g)	H				[7081-38-1]	$162
1490103	Oxyquinoline Sulfate (200 mg)	F-1			F (07/02)	[134-31-6]	$162
1491004	Oxytetracycline (200 mg)	J0C084	913 ug/mg (ai)		I-1 (10/04)	[6153-64-6]	$162
1491300	Oxytocin (5 vials, 46 USP units per vial)	F				[50-56-6]	$162
1491332	Paclitaxel (200 mg)	F0C180				[33069-62-4]	$1,568
1491343	Paclitaxel Related Compound A (20 mg) (Cephalomannine)	F0C179				[71610-00-9]	$784
1491354	Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel)	F0C181				nf	$784

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1491503	Padimate O (300 mg)	H0B154			G (04/03)	[21245-02-3]	$162
1492040	Palm Oil (1 g) (AS)	F0D179				[8002-75-3]	$162
1492007	Palmitic Acid (500 mg)	I				[57-10-3]	$162
1493000	Pamoic Acid (250 mg)	G-4			G-3 (01/03)	[130-85-8]	$162
1494057	Pancreatin Amylase and Protease (2 g)	I			H (10/00)	[8049-47-6]	$162
1494079	Pancreatin Lipase (2 g)	I			H-1 (03/01)	[8049-47-6]	$162
1494501	Panthenol, Racemic (200 mg)	G			F-1 (02/00)	[16485-10-2]	$162
1494807	Pantolactone (500 mg)	F				[599-04-2]	$506
1495005	Papain (1 g)	I0C389	6700 USP units/ mg (ai)		H (06/04) G (12/01)	[9001-73-4]	$162
1496008	Papaverine Hydrochloride (200 mg)	H				[61-25-6]	$162
1497000	Paramethadione (500 mg)	G				[115-67-3]	$162
1498003	Paramethasone Acetate (200 mg)	G			F-1 (05/01)	[1597-82-6]	$162
1498706	Parbendazole (200 mg)	F				[14255-87-9]	$162
1499006	Pargyline Hydrochloride (200 mg)	F-1				[306-07-0]	$162
1500003	Paromomycin Sulfate (125 mg)	G			F-3 (01/01)	[1263-89-4]	$162
1500218	Paroxetine Hydrochloride (350 mg)	G0D003	0.972 mg/mg (ai)		F0B288 (09/04)	[110429-35-1]	$162
1500229	Paroxetine Related Compound A (10 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylene-dioxy)phenoxy]methylpiperidine Hydrochloride)				F1D058 (10/05) F0B172 (07/05)	n/f	$506
1500230	Paroxetine Related Compound B (20 mg) (trans-4-phenyl-3-([(3,4-methylenedioxy)phe-noxy]methylpiperidine acetate)				F0B189 (10/05)	n/f	$506
1500240	Paroxetine Related Compound C (15 mg) ((+)-trans-Paroxetine hydrochloride)	G0D053	0.96 mg/mg (ai)		F0B192 (05/05)	[130855-30-0]	$506
1500251	Paroxetine Related Compound D (15 mg) ((-)-cis-Paroxetine hydrochloride)	F0C228				n/f	$506
1500262	Paroxetine Related Compound E Mixture (25 mg) (1-Methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydorpyridine in Paroxetine Hydrochloride Matrix)	F0D225	0.86 ng/mg (ai)			n/f	$506
1500273	Paroxetine Related Compound F (10 mg) (trans(-)-1-Methyl-3-[(1,3-benzodioxol-5-yloxy)-methyl]-4-(4-fluorophenyl)piperidine)	F0D237	1.00 mg/mg (ai)			n/f	$506
1500284	Paroxetine Related Compound G (10 mg) ((+/-)trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4''-fluorophenyl-4'-phenyl)piperidine hydrochloride)	F0D110	0.99 mg/mg (ai)			n/f	$506
1500400	Parthenolide (25 mg)	F				[20554-84-1]	$162
1500502	Particle Count Set (2 blanks and 2 suspensions)	I			H (09/02)	n/f	$506
1500557	Peanut Oil (1 g) (AS)	F0D171		1		[8002-03-7]	$162
1500808	Penbutolol Sulfate (200 mg)	F				[38363-32-5]	$162
1501006	Penicillamine (200 mg)	H1B164			H (01/04)	[52-67-5]	$162
1501108	Penicillamine Disulfide (100 mg)	H			G (07/00)	[20902-45-8]	$506
1502009	Penicillin G Benzathine (200 mg)	J				[41372-02-5]	$162
1502508	Penicillin G Potassium (200 mg)	J0C349	89.3%/1595 PG units/mg (ai)		I (07/05) H (02/99)	[113-98-4]	$162
1502552	Penicillin G Procaine (200 mg)	G0C271			F-1 (08/04) F (03/99)	[6130-64-9]	$162
1502701	Penicillin G Sodium (200 mg)	L-3			L-2 (09/01)	[69-57-8]	$162
1504489	Penicillin V (200 mg)	F1C318			F (08/05)	[87-08-1]	$162
1504503	Penicillin V Potassium (200 mg)	H0C213			G-1 (06/04) G (06/00)	[132-98-9]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1505007	Pentazocine **CIV** (500 mg)	I0C418	0.998 mg/mg (dr)		H (01/05) G-1 (11/00)	[359-83-1]	$215
1505506	Pentetic Acid (100 mg)	F-1			F (09/01)	[67-43-6]	$162
1507002	Pentobarbital **CII** (200 mg)			6	H3C144 (12/04) H-2 (07/04) H-1 (08/02)	[76-74-4]	$215
1508901	Pentoxifylline (200 mg)	F0B202				[6493-05-6]	$162
1510007	Pepsin (5 g)	F-2				[9001-75-6]	$162
1510801	Perflubron (0.5 mL)	G0C103			F (04/04)	[423-55-2]	$162
1510845	Pergolide Mesylate (200 mg)	F1C225			F (07/04)	[66104-23-2]	$202
1510867	Pergolide Sulfoxide (50 mg)	F0B014				[72822-01-6]	$202
1511000	Perphenazine (200 mg)	J0B249			I (10/03)	[58-39-9]	$162
1511203	Perphenazine Sulfoxide (100 mg)	G-1			G (07/02)	[10078-25-8]	$506
1512002	Phenacemide (250 mg)	F				[63-98-9]	$162
1513005	Phenacetin (500 mg)	H-1			H (09/00)	[62-44-2]	$162
1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)	H3A009			H-2 (02/03) H-1 (06/01)	[62-44-2]	$96
1515000	Phenazopyridine Hydrochloride (200 mg)	H0C426	0.998 mg/mg (dr)		G-4 (12/04)	[136-40-3]	$162
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025			G (12/02)	[956-90-1]	$215
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G			F (01/01)	[50-58-8]	$215
1517006	Phenelzine Sulfate (200 mg)	G			F-1 (04/02)	[156-51-4]	$162
1517301	D-Phenethicillin Potassium (200 mg)	F				n/f	$506
1517607	L-Phenethicillin Potassium (200 mg)	F				n/f	$162
1520000	Phenformin Hydrochloride (200 mg)	G				[834-28-6]	$162
1522006	Phenindione (250 mg)	F				[83-12-5]	$162
1522301	Pheniramine Maleate (100 mg)	F1C342			F (08/04)	[132-20-7]	$162
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2				[1707-14-8]	$215
1524001	Phenobarbital **CIV** (200 mg)	J				[50-06-6]	$215
1524908	Phenolphthalein (250 mg)	F-3				[77-09-8]	$162
1525004	Phenolsulfonphthalein (100 mg)	F-2				[143-74-8]	$162
1525707	Phenothiazine (500 mg) (AS)	F0D231	0.994 mg/mg (dr)			[92-84-2]	$162
1526007	Phenoxybenzamine Hydrochloride (250 mg)	G				[63-92-3]	$162
1526200	Phenoxyethanol (500 mg)	F0D069	0.998 mg/mg (ai)	1		[122-99-6]	$162
1528002	Phensuximide (500 mg)	G			F-1 (03/01)	[86-34-0]	$162
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309			G (08/03)	[1197-21-3]	$215
1529005	Phentolamine Hydrochloride (300 mg)	F				[73-05-2]	$162
1530004	Phentolamine Mesylate (200 mg)	I				[65-28-1]	$162
1530503	L-Phenylalanine (200 mg)	H			G (02/02)	[63-91-2]	$162
1530809	Phenylbenzimidazole Sulfonic Acid (200 mg)	F				[27503-81-7]	$162
1531007	Phenylbutazone (250 mg)	J0A008			I-1 (02/03)	[50-33-9]	$162
1533002	Phenylephrine Hydrochloride (125 mg)	K1C290			K (03/05) J (02/99)	[61-76-7]	$129
1533308	5-Phenylhydantoin (100 mg)	F				[89-24-7]	$506
1533851	Phenylpropanediol (100 mg)	F				n/f	$506
1533909	Phenylpropanolamine Bitartrate (100 mg) **(List Chemical)**	F				[67244-90-0]	$162
1534005	Phenylpropanolamine Hydrochloride (250 mg) **(List Chemical)**	J			I (02/02)	[154-41-6]	$162
1535008	Phenytoin (200 mg)	I2B233			I-1 (03/04) I (04/01)	[57-41-0]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1535507	Phenytoin Sodium (200 mg)	H			G (05/99)	[630-93-3]	$162
1535019	Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine)	F0C155				[3060-50-2]	$506
1535020	Phenytoin Related Compound B (50 mg) (alpha-((aminocarbonyl)amino)-alpha-phenyl benzeneacetic acid)	F0C157				[6802-95-5]	$506
1535700	Phosphated Riboflavin (100 mg)	G1B286			G (07/04)	[6184-17-4]	$129
1537003	Physostigmine Salicylate (200 mg)	H-1			H (06/00)	[57-64-7]	$162
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303			M-1 (07/04) M (09/01)	[84-80-0]	$162
1538505	Pilocarpine (300 mg)	F				[92-13-7]	$162
1538902	Pilocarpine Hydrochloride (200 mg)	I0D055	0.998 mg/mg (dr)		H (09/05)	[54-71-7]	$162
1539009	Pilocarpine Nitrate (200 mg)	I				[148-72-1]	$162
1539508	Pimozide (200 mg)	G				[2062-78-4]	$162
1539701	Pindolol (200 mg)	I0B210			H-1 (12/04)	[13523-86-9]	$162
1541000	Piperacetazine (250 mg)	F				[3819-00-9]	$162
1541500	Piperacillin (500 mg)	H				[66258-76-2]	$162
1541703	Piperazine Adipate (200 mg)	F				[142-88-1]	$162
1541805	Piperazine Citrate (200 mg)	F				[144-29-6]	$162
1541907	Piperazine Dihydrochloride (200 mg)	F				[142-64-3]	$162
1542003	Piperazine Phosphate (200 mg)	F				[14538-56-8]	$162
1543006	Piperidolate Hydrochloride (200 mg)	F				[129-77-1]	$162
1544508	Piroxicam (200 mg)	H1D038	0.998 mg/mg (ai)		H (07/05) G (01/99)	[36322-90-4]	$162
1545205	Plicamycin (50 mg)	H			G (04/00)	[18378-89-7]	$498
1545409	Polacrilex Resin (100 mg)	F				n/f	$162
1545500	Polacrilin Potassium (200 mg)	F-2			F-1 (09/00)	n/f	$162
1546106	Poloxalene (500 mg)	F0C009				[9003-11-6]	$162
1546300	Polydimethylsiloxane (500 mg)	H0C020			G-5 (05/04) G-4 (06/01)	[9016-00-6]	$162
1546707	Polyethylene, High Density (3 strips)	G1D115			G (06/05) F-1 (04/01)	[9002-88-4]	$162
1546809	Polyethylene, Low Density (3 strips)	G1B166			G (06/04) F-2 (12/99)	[9002-88-4]	$162
1546853	Polyethylene Oxide (100 mg)	F-1				[25322-68-3]	$162
1546900	Polyethylene Terephthalate (PET) (3 Strips)	F				[25038-59-9]	$162
1546922	Polyethylene Terephthalate G (PETG) (3 Strips)	F				[25640-14-6]	$162
1547007	Polymyxin B Sulfate (200 mg)	K			J-1 (09/99)	[1405-20-5]	$162
1547404	Polyoxyl 50 Stearate (200 mg)	F				[9004-99-3]	$162
1547903	Polyoxyl 40 Stearate (200 mg)	F-2			F-1 (05/00)	[9004-99-3]	$162
1547925	Polysorbate 20 (2 g) (AS)	F0D130				[9005-64-5]	$162
1547936	Polysorbate 40 (2 g) (AS)	F0D204				[9005-66-7]	$162
1547947	Polysorbate 60 (2 g) (AS)	F0D131				[9005-67-8]	$162
1547969	Polysorbate 80 (2 g) (AS)	F0D132				[9005-65-6]	$162
1548000	Polythiazide (200 mg)	F-1				[346-18-9]	$162
1548101	Potassium Benzoate (1 g) (AS)	F0D161	0.999 mg/mg (an)			[582-25-2]	$162
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	99.9% (dr)			[298-14-6]	$162
1548167	Potassium Carbonate (1 g) (AS)	F0D075	99.8% (dr)			[584-08-7]	$162
1548190	Potassium Chloride (1 g) (AS)	F0D127	100.0% (dr)			[7447-40-7]	$162
1550001	Potassium Gluconate (200 mg)	H0C064			G (06/04)	[299-27-4]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1551004	Potassium Guaiacolsulfonate (500 mg)	J0B292			I-1 (07/03) I (11/00)	[78247-49-1]	$162
1548280	Potassium Iodide (1 g) (AS)	F0D078	100.0% (dr)			[7681-11-0]	$162
1548407	Potassium Sorbate (1 g) (AS)	F0D264	99.6% (dr)	1		[24634-61-5]	$162
1551150	Potassium Sucrose Octasulfate (300 mg)	I0B283			H0B119 (04/04) G-1 (04/03) G (02/01)	[76578-81-9]	$162
1551300	Potassium Trichloroammineplatinate (20 mg)	I0D022	0.84 mg/mg (dr)		H0B149 (12/04) G-1 (01/03) G (07/99)	[13820-91-2]	$506
1551503	Povidone (100 mg)	F-1			F (11/01)	[9003-39-8]	$162
1553000	Pralidoxime Chloride (200 mg)	G-2			G-1 (03/01) G (08/99)	[51-15-0]	$162
1554002	Pramoxine Hydrochloride (500 mg)	I1D197	0.998 mg/mg (dr)	2	I (10/05) H (11/02)	[637-58-1]	$162
1554501	Prazepam **CIV** (500 mg)	G0C066			F-1 (11/02)	[2955-38-6]	$215
1554603	Praziquantel (200 mg)	G			F-3 (07/02) F-2 (09/00)	[55268-74-1]	$162
1554658	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	$506
1554669	Praziquantel Related Compound B (50 mg) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one)	F-2			F-1 (06/00)	n/f	$506
1554670	Praziquantel Related Compound C (50 mg) (2-(N-formylhexahydrohippuroyl)-1,2,3,4-tetrahydroisoquinolin-1-one)	F-2			F-1 (06/00)	n/f	$506
1554705	Prazosin Hydrochloride (500 mg)	H0B254			G-1 (02/05) G (02/01)	[19237-84-4]	$162
1555005	Prednisolone (200 mg)	M			L-1 (04/02)	[50-24-8]	$162
1556008	Prednisolone Acetate (200 mg)	J			I-1 (02/02)	[52-21-1]	$162
1556507	Prednisolone Hemisuccinate (125 mg)	H-1			H (02/99)	[2920-86-7]	$129
1558003	Prednisolone Tebutate (200 mg)	F				[7681-14-3]	$162
1559006	Prednisone (250 mg)	L1B251			L (11/04) K-1 (01/02) K (02/00)	[53-03-2]	$162
1559505	Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets)	O0C056			N (06/04) M (09/02) L (11/00)	[53-03-2]	$187
1561008	Prilocaine Hydrochloride (200 mg)	F3B215			F-2 (03/04)	[1786-81-8]	$162
1561507	Primaquine Phosphate (200 mg)	F-1				[63-45-6]	$162
1562000	Primidone (200 mg)	G			F-6 (04/99)	[125-33-7]	$162
1563003	Probenecid (200 mg)	I0A011			H-1 (03/03)	[57-66-9]	$162
1563309	Probucol (200 mg)	G			F-1 (01/02)	[23288-49-5]	$162
1563320	Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-*tert*-butyldiphenoquinone)	F-2			F-1 (11/04)	n/f	$506
1563331	Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-*tert*-butylphenol))	F-2			F-1 (08/03)	n/f	$506
1563342	Probucol Related Compound C (25 mg) (4-[(3,5-di-*tert*-butyl-2-hydroxyphenylthio)isopropylidenethio]-2,6-di-*tert*-butylphenol)	F-2			F-1 (05/00)	n/f	$506
1563502	Procainamide Hydrochloride (200 mg)	H1B117			H (04/03)	[614-39-1]	$162
1564006	Procaine Hydrochloride (200 mg)	H				[51-05-8]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1565009	Procarbazine Hydrochloride (200 mg)	F				[366-70-1]	$162
1566001	Prochlorperazine Maleate (200 mg)	H-1				[84-02-6]	$162
1567004	Procyclidine Hydrochloride (200 mg)	G				[1508-76-5]	$162
1568007	Progesterone (200 mg)	H6C088			H-5 (11/04) H-4 (07/02)	[57-83-0]	$129
1568506	L-Proline (200 mg)	G0D146	1.00 mg/mg (dr)		F-2 (09/05) F-1 (01/02)	[147-85-3]	$162
1569000	Promazine Hydrochloride (200 mg)	H0B261			G (10/03)	[53-60-1]	$162
1570009	Promethazine Hydrochloride (500 mg)	K			J-1 (10/00)	[58-33-3]	$162
1570304	Propafenone Hydrochloride (200 mg)	G1C184			G (12/04) F-1 (01/01)	[34183-22-7]	$162
1570508	Propantheline Bromide (200 mg)	I0A019			H (11/02)	[50-34-0]	$162
1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)	G0B258			F-1 (12/03)	n/f	$506
1571001	Proparacaine Hydrochloride (200 mg)	G				[5875-06-9]	$162
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	99.8 % w/w (ai)			[79-09-4]	$162
1573007	Propoxycaine Hydrochloride (200 mg)	F				[550-83-4]	$162
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285			K (09/04)	[1639-60-7]	$215
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	0.993 mg/mg (an)		H (05/05)	[26570-10-5]	$215
1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)	G-5				n/f	$506
1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)	H0D012	0.94 mg/mg (ai)		G-3 (05/05)	n/f	$506
1576005	Propranolol Hydrochloride (200 mg)	I0C170			H-1 (12/04) H (09/01)	[318-98-9]	$162
1576504	Propylene Carbonate (200 mg)	F				[108-32-7]	$162
1576708	Propylene Glycol (1 mL)	I0C022			H (03/04) G (02/99)	[57-55-6]	$162
1576720	Propylene Glycol Diacetate (250 mg)				F (09/05)	[623-84-7]	$162
1576800	Propyl Gallate (200 mg)	G-1			G (01/03)	[121-79-9]	$162
1577008	Propylparaben (200 mg)	I			H (02/00)	[94-13-3]	$162
1578000	Propylthiouracil (200 mg)	G			F-1 (01/00)	[51-52-5]	$162
1578500	Prostaglandin A1 (25 mg)	H0B108			G (04/03)	[14152-28-4]	$550
1580002	Protriptyline Hydrochloride (200 mg)	F-1				[1225-55-4]	$162
1581005	Pseudoephedrine Hydrochloride (125 mg) **(List Chemical)**	J1B203			J (01/04) I (05/02)	[345-78-8]	$129
1581504	Pseudoephedrine Sulfate (200 mg) **(List Chemical)**	G1C135			G (06/04) F-2 (05/02)	[7460-12-0]	$162
1584003	Pyrantel Pamoate (1 g)	I			H-1 (04/00)	[22204-24-6]	$162
1585006	Pyrazinamide (200 mg)	G			F-2 (02/00)	[98-96-4]	$162
1586009	Pyridostigmine Bromide (200 mg)	I0C324	0.999 mg/mg (dr)		H (01/05)	[101-26-8]	$162
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P			O-1 (04/00)	[58-56-0]	$162
1588004	Pyrilamine Maleate (200 mg)	I0B276			H (12/03)	[59-33-6]	$162
1589007	Pyrimethamine (200 mg)	H			G (07/02)	[58-14-0]	$162
1592001	Pyrvinium Pamoate (500 mg)	G				[3546-41-6]	$162
1592205	Quazepam **CIV** (200 mg)	F				[36735-22-5]	$215
1592227	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	$506

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1592409	Quercetin (500 mg)	F0B015				[6151-25-3]	$162
1593004	Quinacrine Hydrochloride (200 mg)	F-1				[6151-30-0]	$162
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				[103733-49-9]	$506
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				[85441-60-7]	$506
1594007	Quinethazone (1.5 g)	G				[73-49-4]	$162
1594506	Quinic Acid (200 mg)	F				[77-95-2]	$162
1595000	Quinidine Gluconate (200 mg)	H1A028			H (04/03)	[7054-25-3]	$162
1595509	Quinidine Sulfate (500 mg)	H-1			H (12/99)	[6591-63-5]	$162
1596807	Quinine Hydrochloride Dihydrate (1 g)	F0C108				[6119-47-7]	$162
1597005	Quinine Sulfate (200 mg)	H				[6119-70-6]	$162
1597504	Quininone (50 mg)	H0B034			G-1 (03/04)	[84-31-1]	$506
1598008	3-Quinuclidinyl Benzilate (25 mg) (FOR U.S. SALE ONLY)	H			G (11/01)	[6581-06-2]	$536
1598303	Ramipril (200 mg)	F0C099				[87333-19-5]	$162
1598314	Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid)	F0C100				[91224-69-0]	$506
1598405	Ranitidine Hydrochloride (200 mg)	H0B268			G (01/04)	[66357-59-3]	$162
1598507	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]	$506
1598609	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]	$506
1598700	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]	$506
1599000	Rauwolfia Serpentina (15 g)	G				[8063-17-0]	$162
1599500	Powdered Red Clover Extract (500 mg)	F0C188				n/f	$270
1600813	Repaglinide (200 mg)	F0B265				[135062-02-1]	$162
1600824	Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N-acetyl-L-glutamate salt)	F0B267				n/f	$506
1600835	Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid)	F0B269				[99469-99-5]	$506
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]	$506
1601000	Reserpine (200 mg)	O0C106			N (06/03)	[50-55-5]	$162
1601102	Residual Solvents Mixture - Class 1 (1.2 mL/ampule; 3 ampules)	F0C407				n/f	$162
1601146	Residual Solvent Class 1 - Benzene (1.2 mL/ampule; 3 ampules)	F0C408	10.1 mg/mL (ai)			n/f	$162
1601168	Residual Solvent Class 1 - Carbon Tetrachloride (1.2 mL/ampule; 3 ampules)	F0C409	19.7 mg/mL (ai)			n/f	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1601180	Residual Solvent Class 1 - 1,2-Dichloroethane (1.2 mL/ampule; 3 ampules)	F0C412	25.1 mg/mL (ai)			n/f	$162
1601204	Residual Solvent Class 1 - 1,1-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0C411	37.9 mg/mL (ai)			n/f	$162
1601226	Residual Solvent Class 1 - 1,1,1-Trichloroethane (1.2 mL/ampule; 3 ampules)	F0C410	49.1 mg/mL (ai)			n/f	$162
1601281	Residual Solvents Class 2 - Mixture A (1.2 mL/ampule; 3 ampules)	F0D051				n/f	$162
1601306	Residual Solvent Class 2 - Mixture C (1.2 mL/ampule; 3 ampules)	F0D182				n/f	$162
1601340	Residual Solvent Class 2 - Acetonitrile (1.2 mL/ampule; 3 ampules)	F0D049	2.00 mg/mL (ai)			n/f	$162
1601361	Residual Solvent Class 2 - Chlorobenzene (1.2 mL/ampule; 3 ampules)	F0D048	1.81 mg/mL (ai)			n/f	$162
1601383	Residual Solvent Class 2 - Chloroform (1.2 mL/ampule; 3 ampules)	F0D186	0.293 mg/mL (ai)			n/f	$162
1601408	Residual Solvent Class 2 - Cyclohexane (1.2 mL/ampule; 3 ampules)	F0D047	18.0 mg/mL (ai)			n/f	$162
1601420	Residual Solvent Class 2 - 1,2-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0D040	9.2 mg/mL (ai)			n/f	$162
1601463	Residual Solvent Class 2 - 1,2-Dimethoxyethane (1.2 mL/ampule; 3 ampules)	F0D185	0.479 mg/mL (ai)			n/f	$162
1601485	Residual Solvent Class 2 - N,N-Dimethylacetamide (1.2 mL/ampule; 3 ampules)	F0D169	5.44 mg/mL (ai)			n/f	$162
1601500	Residual Solvent Class 2 - N,N-Dimethylformamide (1.2 mL/ampule; 3 ampules)	F0D189	4.42 mg/mL (ai)			n/f	$162
1601521	Residual Solvent Class 2 - 1,4-Dioxane (1.2 mL/ampule; 3 ampules)	F0D050	1.89 mg/mL (ai)			n/f	$162
1601543	Residual Solvent Class 2 - 2-Ethoxyethanol (1.2 mL/ampule; 3 ampules)	F0D195	0.80 mg/mL (ai)			n/f	$162
1601565	Residual Solvent Class 2 - Ethylene Glycol (1.2 mL/ampule; 3 ampules)	F0D191	3.07 mg/mL (ai)			n/f	$162
1601587	Residual Solvent Class 2 - Formamide (1.2 mL/ampule; 3 ampules)	F0D188	1.10 mg/mL (ai)			n/f	$162
1601623	Residual Solvent Class 2 - Methanol (1.2 mL/ampule; 3 ampules)	F0D045	14.8 mg/mL (ai)			n/f	$162
1601645	Residual Solvent Class 2 - 2-Methoxyethanol (1.2 mL/ampule; 3 ampules)	F0D194	0.253 mg/mL (ai)			n/f	$162
1601667	Residual Solvent Class 2 - Methylbutylketone (1.2 mL/ampule; 3 ampules)	F0D202	0.248 mg/mL (ai)			n/f	$162
1601689	Residual Solvent Class 2 - Methylcyclohexane (1.2 mL/ampule; 3 ampules)	F0D044	5.46 mg/mL (ai)			n/f	$162
1601441	Residual Solvent Class 2 - Methylene Chloride (1.2 mL/ampule; 3 ampules)	F0D046	2.90 mg/mL (ai)			n/f	$162
1601703	Residual Solvent Class 2 - N-Methylpyrrolidone (1.2 mL/ampule; 3 ampules)	F0D183	2.63 mg/mL (ai)			n/f	$162
1601725	Residual Solvent Class 2 - Nitromethane (1.2 mL/ampule; 3 ampules)	F0D210	0.248 mg/mL (ai)			n/f	$162
1601747	Residual Solvent Class 2 - Pyridine (1.2 mL/ampule; 3 ampules)	F0D215	0.99 mg/mL (ai)			n/f	$162
1601769	Residual Solvent Class 2 - Sulfolane (1.2 mL/ampule; 3 ampules)	F0D187	0.80 mg/mL (ai)			n/f	$162
1601770	Residual Solvent Class 2 - Tetrahydrofuran (1.2 mL/ampule; 3 ampules)	F0D043	3.49 mg/mL (ai)			n/f	$162

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1601780	Residual Solvent Class 2 - Tetralin (1.2 mL/ampule; 3 ampules)	F0D228	0.493 mg/mL (ai)			n/g	$162
1601805	Residual Solvent Class 2 - Toluene (1.2 mL/ampule; 3 ampules)	F0D042	4.39 mg/mL (ai)			n/f	$162
1601827	Residual Solvent Class 2 - Trichloroethylene (1.2 mL/ampule; 3 ampules)	F0D221	0.391 mg/mL (ai)			n/f	$162
1601849	Residual Solvent Class 2 - Xylenes (1.2 mL/ampule; 3 ampules)	F0D041	10.7 mg/mL (ai)			n/f	$162
1602003	Resorcinol (200 mg)	I0D135	0.998 mg/mg (ai)	2	H-1 (10/05) H (04/01)	[108-46-3]	$162
1602706	Ribavirin (200 mg)	H1C335			H (03/05) G (08/01)	[36791-04-5]	$301
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021			M-1 (09/04) M (11/00)	[83-88-5]	$162
1603800	Rifabutin (50 mg)	G0B040			F (11/02)	[72559-06-9]	$162
1604009	Rifampin (300 mg)	J			I (09/00)	[13292-46-1]	$162
1604202	Rifampin Quinone (50 mg)	H			G (12/01)	[13983-13-6]	$506
1604508	Rimantadine Hydrochloride (300 mg)	F0C266				[1501-84-4]	$162
1604600	Rimexolone (100 mg)	F				[49697-38-3]	$162
1604701	Ritodrine Hydrochloride (200 mg)	G-1				[23239-51-2]	$162
1606208	Roxarsone (200 mg)	F				[121-19-7]	$162
1606503	Rutin (100 mg)	G0C355		2	F (09/05)	[153-18-4]	$162
1607007	Saccharin (200 mg)	G-3			G-2 (12/01)	[81-07-2]	$162
1608000	Salicylamide (200 mg)	F-4			F-3 (05/03)	[65-45-2]	$162
1609002	Salicylic Acid (125 mg)	J2B147			J-1 (10/03) J (10/02) I (07/99)	[69-72-7]	$129
1609501	Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets)	O			N (02/02)	[69-72-7]	$162
1609807	Salsalate (125 mg)	G				[552-94-3]	$129
1609829	Saquinavir Mesylate (200 mg)	F0B008				[149845-06-7]	$162
1609831	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	$506
1610001	Scopolamine Hydrobromide (250 mg)	J0B051			I-1 (01/03)	[6533-68-2]	$162
1610090	Scopoletin (20 mg)	F0C329				[92-61-5]	$162
1611004	Secobarbital **CII** (200 mg)	H				[76-73-3]	$215
1611900	Selegiline Hydrochloride (200 mg)	G				[14611-52-0]	$162
1611955	Selenomethionine (100 mg)	F0B006				[1464-42-2]	$162
1612007	Sennosides (250 mg)	H1B223			H (04/04)	[81-27-6] (A) [128-57-4] (B)	$162
1612506	L-Serine (200 mg)	G			F-3 (11/00)	[56-45-1]	$162
1612540	Sevoflurane (1 mL)	F0C219				[28523-86-6]	$162
1612550	Sevoflurane Related Compound A (0.2 mL) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether)	F0C261				[58109-34-5]	$506
1612594	Sevoflurane Related Compound C (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-propanol)	F0D142	1.00 mg/mg (ai)	1		[920-66-1]	$506
1612608	Silver Sulfadiazine (200 mg)	I			H (04/01)	[22199-08-2]	$162
1612630	Silybin (50 mg)	F				[22888-70-6]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1612641	Silydianin (20 mg)	F				[29782-68-1]	$162
1612652	Simethicone (50 g)	H0D084	5.3% SiO2 (ai)		G (11/04) F (07/00)	[8050-81-5]	$162
1612700	Simvastatin (200 mg)	H1B093			H (07/03) G (02/02) F-1 (05/99)	[79902-63-9]	$162
1612801	Sisomicin Sulfate (500 mg)	I0C238			H (04/04) G (10/00)	[53179-09-2]	$162
1613407	Sodium Acetate (1 g) (AS)	F0D083	99.8% (dr)			[127-09-3]	$162
1613509	Sodium Ascorbate (200 mg)	G2C067			G-1 (03/05)	[134-03-2]	$162
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	99.7% (dr)	1		[144-55-8]	$162
1613600	Sodium Butyrate (25 mg)	F				[156-54-7]	$162
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	100.0% (dr)			[497-19-8]	$162
1613804	Sodium Chloride (1 g) (AS)	F0D269	100.0% (ai)	1		[7647-14-5]	$162
1613859	Sodium Citrate (1 g) (AS)	F0D172	100.0% (an)			[6132-04-3]	$162
1614002	Sodium Fluoride (1 g) (FOR U.S. SALE ONLY)	H-1			H (05/01)	[7681-49-4]	$162
1614308	Sodium Lactate (200 mg)	I0C299			H (04/05) G (06/00)	[867-56-1]	$162
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	98.6% (ai)			[7681-57-4]	$162
1614454	Sodium Nitrite (1 g) (AS)	F0D117	99.6% (dr)			[7632-00-0]	$162
1614501	Sodium Nitroprusside (500 mg)	H			G (11/99)	[13755-38-9]	$162
1614603	Sodium Propionate (200 mg)	F-1			F (03/02)	[6700-17-0]	$162
1614669	Sodium Starch Glycolate (400 mg)	F0C087				[9063-38-1]	$162
1614705	Sodium Stearyl Fumarate (200 mg)	G			F-2 (05/01)	[4070-80-8]	$162
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	99.8% (dr)			[7757-82-6]	$162
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	100.2% (an)			[10102-17-7]	$162
1616008	1,4-Sorbitan (200 mg)	I0A003			H (04/03) G (02/00)	[27299-12-3]	$162
1617000	Sorbitol (125 mg)	H1B139			H (01/04)	[50-70-4]	$129
1617408	Sotalol Hydrochloride (300 mg)	F0C234				[959-24-0]	$189
1617419	Sotalol Related Compound A (50 mg) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride)	F0C235				n/f	$506
1617420	Sotalol Related Compound B (50 mg) (N-(4-Formylphenyl)methanesulfonamide)	F0C236				n/f	$506
1617430	Sotalol Related Compound C (50 mg) (N-[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride)	F0C237				n/f	$506
1618003	Spectinomycin Hydrochloride (200 mg)	G0C310	650 ug/mg (ai)		F-2 (01/05)	[22189-32-8]	$162
1619006	Spironolactone (125 mg)	J-1				[52-01-7]	$129
1619505	Squalane (500 mg)	G-1				[111-01-3]	$162
1620005	Stanozolol **CIII** (200 mg)	F-3			F-2 (02/01)	[10418-03-8]	$215
1621008	Stearic Acid (500 mg)	J			I (10/01)	[57-11-4]	$162
1621507	Stearoyl Polyoxyglycerides (100 mg)	F0C286				n/f	$162
1622000	Stearyl Alcohol (125 mg)	H2B217			H-1 (12/04) H (09/99)	[112-92-5]	$129
1623003	Streptomycin Sulfate (200 mg)	J0B195			I (04/03)	[3810-74-0]	$162
1623502	Succinylcholine Chloride (500 mg)	H				[71-27-2]	$162
1623604	Succinylmonocholine Chloride (150 mg)	G			F-1 (02/01)	n/f	$506
1623626	Sucralose (400 mg)	G0B028			F (04/03)	[56038-13-2]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1623637	Sucrose (100 mg)	H1C223			H0B002 (11/04) G-1 (03/03) G (05/99)	[57-50-1]	$162
1623648	Sufentanil Citrate **CII** (25 mg)	H0B208			G (05/03) F-1 (04/02) F (09/99)	[60561-17-3]	$229
1623670	Sulbactam (250 mg)	H0C396	0.976 mg/mg (ai)		G (05/05) F-1 (05/00)	[68373-14-8]	$162
1623681	Sulconazole Nitrate (200 mg)	F-1			F (05/02)	[61318-91-0]	$162
1623706	Sulfabenzamide (200 mg)	G				[127-71-9]	$162
1623808	Sulfacetamide (300 mg)	G-1				[144-80-9]	$162
1624006	Sulfacetamide Sodium (500 mg)	I1B318			I (09/04) H (08/01)	[6209-17-2]	$162
1624505	Sulfachlorpyridazine (200 mg)	F				[80-32-0]	$162
1625009	Sulfadiazine (200 mg)	J			I (03/04)	[68-35-9]	$162
1626001	Sulfadimethoxine (200 mg)	G0D249	0.998 mg/mg (ai)	2	F4C298 (09/05) F-3 (11/04) F-2 (03/99)	[122-11-2]	$162
1626500	Sulfadoxine (200 mg)	F3C336	0.999 mg/mg (ai)	2	F-2 (10/05) F-1 (07/02)	[2447-57-6]	$162
1628007	Sulfamerazine (500 mg)	H1C171			H (12/04)	[127-79-7]	$162
1629000	Sulfamethazine (1 g)	G-3				[57-68-1]	$162
1630009	Sulfamethizole (200 mg)	F-3			F-2 (01/03)	[144-82-1]	$162
1631001	Sulfamethoxazole (200 mg)	I-1			I (04/02)	[723-46-6]	$162
1631500	Sulfamethoxazole N4-glucoside (25 mg)	H			G (11/01)	n/f	$506
1632004	Sulfanilamide (5 g)	O0B047			N (01/04)	[63-74-1]	$162
1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)	K0B133			J-1 (03/04) J (09/99)	[63-74-1]	$78
1633506	Sulfanilic Acid (200 mg)	G			F-2 (09/00)	[121-57-3]	$506
1634000	Sulfapyridine (200 mg)	I0B298			H (07/04)	[144-83-2]	$162
1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)	J			I (07/00)	[144-83-2]	$96
1635206	Sulfaquinoxaline (200 mg)	F0A005				[59-40-5]	$162
1636005	Sulfasalazine (125 mg)	G-2			G-1 (06/99)	[599-79-1]	$129
1636504	Sulfathiazole (350 mg)	H			G (08/00)	[72-14-0]	$162
1637008	Sulfinpyrazone (200 mg)	H0C416	0.992 mg/mg (ai)		G (03/05)	[57-96-5]	$162
1638000	Sulfisoxazole (200 mg)	J			I-1 (06/99)	[127-69-5]	$162
1639003	Sulfisoxazole Acetyl (200 mg)	H-1				[80-74-0]	$162
1640002	Sulfisoxazole Diolamine (500 mg)	F				[4299-60-9]	$162
1642008	Sulindac (200 mg)	H			G-1 (12/01)	[38194-50-2]	$162
1642154	Sumatriptan (50 mg)	F0C220				[103628-46-2]	$216
1642201	Sumatriptan Succinate (200 mg)	F0C231				[103628-48-4]	$216
1642212	Sumatriptan Succinate Related Compound A (15 mg) ([3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]-N-methylmethansulfonamide, succinate salt)	F0C221				n/f	$649
1642223	Sumatriptan Succinate Related Compound C (50 mg) ([3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt)	F0C230				n/f	$649
1642507	Suprofen (200 mg)	F				[40828-46-4]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1642700	Tacrine Hydrochloride (500 mg)	F0C119				[1684-40-8]	$162
1643000	Talbutal **CIII** (250 mg)	F				[115-44-6]	$215
1643306	Tamoxifen Citrate (200 mg)	H			G-2 (09/01) G-1 (05/00)	[54965-24-1]	$162
1643361	Taurine (100 mg)	F0C104				[107-35-7]	$162
1643408	Temazepam **CIV** (200 mg)	H0C205			G (06/04) F (12/99)	[846-50-4]	$215
1643452	Terazosin Hydrochloride (200 mg)	F0C244				[70024-40-7]	$162
1643463	Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C245				n/f	$506
1643474	Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine)	F0C218				n/f	$506
1643485	Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C257				n/f	$506
1643500	Terbutaline Sulfate (125 mg)	H			G (04/99)	[23031-32-5]	$129
1643703	Terconazole (200 mg)	G3C322			G-2 (08/05) G-1(04/01) G (03/99)	[67915-31-5]	$162
1643805	Terfenadine (200 mg)	H			G (12/99)	[50679-08-8]	$162
1643907	Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone)	G				n/f	$506
1643929	Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide)	F				n/f	$506
1644003	Terpin Hydrate (750 mg)	G				[2451-01-6]	$162
1645006	Testolactone **CIII** (125 mg)	F-1				[968-93-4]	$172
1646009	Testosterone **CIII** (125 mg)	I1B253			I (08/04)	[58-22-0]	$172
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	1.000 mg/mg (ai)		G-1 (03/05) G (08/01)	[58-20-8]	$215
1648004	Testosterone Enanthate **CIII** (200 mg)	J				[315-37-7]	$215
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005			L (08/04) K-1 (11/01)	[57-85-2]	$215
1650006	Tetracaine Hydrochloride (200 mg)	J				[136-47-0]	$162
1651009	Tetracycline Hydrochloride (200 mg)	L0C216	976 ug/mg (ai)		K (12/04)	[64-75-5]	$162
1652001	Tetrahydrozoline Hydrochloride (200 mg)	G1A015			G (03/03)	[522-48-5]	$162
1652500	Thalidomide (200 mg)	F0C107				[50-35-1]	$189
1653004	Theophylline (200 mg)	J0B180			I (01/04)	[58-55-9]	$162
1655000	Thiabendazole (100 mg)	G0A027			F-1 (04/03) F (04/01)	[148-79-8]	$162
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O			N (11/02) M-1 (04/99)	[67-03-8]	$162
1656308	Thiamylal **CIII** (200 mg)	F				[77-27-0]	$215
1657005	Thiethylperazine Malate (200 mg)	G			F-1 (09/00)	[52239-63-1]	$162
1658008	Thiethylperazine Maleate (200 mg)	F-1				[1179-69-7]	$162
1659000	Thimerosal (500 mg)	H1B205			H (09/04) G (12/99)	[54-64-8]	$162
1660000	Thioguanine (200 mg)	F-1				[154-42-7]	$162
1661002	Thiopental **CIII** (250 mg)	I1D198	1.000mg/mg (dr)	2	I (09/05)	[76-75-5]	$215
1662504	Thioridazine (200 mg)	H				[50-52-2]	$162

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1663008	Thioridazine Hydrochloride (200 mg)	H				[130-61-0]	$162
1663700	Thiostrepton (200 mg)	F1B022			F (11/02)	[1393-48-2]	$162
1664000	Thiotepa (500 mg)	I			H (01/99)	[52-24-4]	$162
1665003	Thiothixene (250 mg)	G				[3313-26-6]	$162
1666006	(E)-Thiothixene (100 mg)	H			G-1 (05/00)	[3313-27-7]	$506
1667100	Thonzonium Bromide (200 mg)	F				[553-08-2]	$162
1667202	L-Threonine (200 mg)	G			F-3 (12/00)	[72-19-5]	$162
1667290	Tiamulin Fumarate (250 mg)	F0C327				[55297-96-6]	$162
1667337	Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin)	F0C328				n/f	$514
1667304	Ticarcillin Monosodium Monohydrate (200 mg)	H			G-1 (03/99)	[74682-62-5]	$162
1667359	Tiletamine Hydrochloride (200 mg)	F0C019				[14176-50-2]	$162
1667406	Timolol Maleate (200 mg)	G-1				[26921-17-5]	$162
1667520	Tinidazole (200 mg)	F0C093				[19387-91-8]	$162
1667530	Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole)	F0C091				[696-23-1]	$506
1667439	Tioconazole (200 mg)	H			G (04/02)	[65899-73-2]	$162
1667450	Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride)	G				n/f	$506
1667461	Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$506
1667472	Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$506
1667585	Titanium Dioxide (1 g) (AS)	F0D079	99.6% (dr)			[13463-67-7]	$162
1667508	Tobramycin (250 mg)	K0B248			J (08/03)	[32986-56-4]	$162
1667552	Tocainide Hydrochloride (125 mg)	F-1			F (04/99)	[35891-93-1]	$129
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M			L-1 (01/00)	[10191-41-0]	$162
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K			J (06/99)	[7695-91-2]	$162
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	G0D077	0.978 mg/mg GC 0.972 mg/mg HPLC (ai)		F-5 (05/05) F-4 (01/02)	[4345-03-3]	$162
1668001	Tolazamide (200 mg)	G-2			G-1 (06/00)	[1156-19-0]	$162
1669004	Tolazoline Hydrochloride (300 mg)	F				[59-97-2]	$162
1670003	Tolbutamide (200 mg)	I			H (06/00)	[64-77-7]	$162
1670207	Tolcapone (200 mg)	F0D280	0.999 mg/mg (ai)	1		[134308-13-7]	$162
1670218	Tolcapone Related Compound A (25 mg) (4'-methyl-3,4-dihydroxybenzophenone)	F0D282		1		n/f	$506
1670502	Tolmetin Sodium (500 mg)	I0B064			H (09/03)	[64490-92-2]	$162
1671006	Tolnaftate (200 mg)	J0C405	1.000 mg/mg (dr)		I (02/05)	[2398-96-1]	$162
1672009	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)	$506
1672304	Torsemide (200 mg)	F0B090				[56211-40-6]	$162
1672315	Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B071				n/f	$506
1672326	Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)a-mino]-3-pyridinesulfonamide)	F0B083				n/f	$506

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1672337	Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B078				n/f	$506
1672803	Transplatin (25 mg)	H0B287			G (03/04)	[14913-33-8]	$506
1673500	Trazodone Hydrochloride (200 mg)	F-2				[25332-39-2]	$162
1674004	Tretinoin (30 mg/ampule; 5 ampules)	I2B185			I-1 (01/04) I (01/02) H (06/01)	[302-79-4]	$162
1675007	Triacetin (1 g)	H0C413			G-1 (02/05) G (06/01)	[102-76-1]	$162
1676000	Triamcinolone (250 mg)	H-1				[124-94-7]	$162
1677002	Triamcinolone Acetonide (500 mg)	K			J (03/99)	[76-25-5]	$162
1678005	Triamcinolone Diacetate (200 mg)	G				[67-78-7]	$162
1679008	Triamcinolone Hexacetonide (125 mg)	G				[5611-51-8]	$129
1680007	Triamterene (200 mg)	I				[396-01-0]	$162
1680506	Triazolam **CIV** (200 mg)	H0B041			G-1 (03/03)	[28911-01-5]	$215
1680608	Tributyl Citrate (500 mg)	G0C227			F (01/05)	[77-94-1]	$162
1680801	Trichlorfon (200 mg)	F				[52-68-6]	$162
1681000	Trichlormethiazide (200 mg)	H				[133-67-5]	$162
1682206	Triclosan (200 mg)	G0D001	0.997 mg/mg (ai)		F0B135 (05/05)	[3380-34-5]	$162
1683005	Tridihexethyl Chloride (200 mg)	F-1				[4310-35-4]	$162
1683504	Trientine Hydrochloride (125 mg)	F2B257			F-1 (09/03) F (08/96)	[38260-01-4]	$129
1683606	Triethyl Citrate (500 mg)	G0C393		2	F-1 (10/05) F (03/02)	[77-93-0]	$162
1685000	Trifluoperazine Hydrochloride (200 mg)	H0A010			G (03/03)	[440-17-5]	$162
1685500	2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone (25 mg)	F				n/f	$506
1686003	Triflupromazine Hydrochloride (200 mg)	F-2			F-1 (03/04)	[1098-60-8]	$162
1686309	Trifluridine (200 mg)	F				[70-00-8]	$187
1686310	Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine)	F				[14599-46-3]	$506
1687006	Trihexyphenidyl Hydrochloride (200 mg)	J			I (07/01)	[52-49-3]	$162
1689001	Trimeprazine Tartrate (200 mg)	F-3			F-2 (08/01)	[4330-99-8]	$162
1690000	Trimethadione (200 mg)	G				[127-48-0]	$162
1692006	Trimethobenzamide Hydrochloride (500 mg)	H-2			H-1 (06/02)	[554-92-7]	$162
1692505	Trimethoprim (300 mg)	J0B228			I (01/04)	[738-70-5]	$162
1693009	Trioxsalen (200 mg)	H0C278			G (04/04)	[3902-71-4]	$162
1694001	Tripelennamine Citrate (200 mg)	G			F (02/03)	[6138-56-3]	$162
1695004	Tripelennamine Hydrochloride (200 mg)	J				[154-69-8]	$162
1696007	Triprolidine Hydrochloride (500 mg)	I			H-1 (02/02)	[6138-79-0]	$162
1696109	Triprolidine Hydrochloride Z-Isomer (100 mg)	G			F-1 (02/02)	n/f	$506
1696200	Trisalicylic Acid (100 mg)	G			F-1 (10/99)	n/f	$506
1697000	Troleandomycin (250 mg)	F-1				[2751-09-9]	$162
1698002	Tromethamine (125 mg)	G			F-3 (07/99)	[77-86-1]	$129
1699005	Tropicamide (125 mg)	G-1			G (02/99)	[1508-75-4]	$129
1700002	Trypsin Crystallized (300 mg)	H			G (12/99)	[9002-07-7]	$162
1700501	L-Tryptophan (200 mg)	G-1			G (09/00)	[73-22-3]	$162
1702008	Tubocurarine Chloride (250 mg)	K-1				[6989-98-6]	$162
1703805	Tylosin (250 mg)	F0C008				[1401-69-0]	$162

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1704003	Tyloxapol (600 mg)	H			G (02/00)	[25301-02-4]	$162
1704502	Tyropanoate Sodium (500 mg)	F				[7246-21-1]	$162
1705006	L-Tyrosine (500 mg)	K0C141	1.00 mg/mg (ai)		J (05/05)	[60-18-4]	$162
1705301	Ubidecarenone (200 mg)	F0B191				[303-98-0]	$260
1705312	Ubidecarenone for System Suitability (25 mg)	F0B194				[303-98-0]	$506
1705505	Undecylenic Acid (200 mg)	G2C018			G-1 (11/04) G (01/02)	[112-38-9]	$162
1705800	Uracil Arabinoside (50 mg)	G			F-1 (06/99)	[3083-77-0]	$162
1706009	Uracil Mustard (500 mg) (FOR U.S. SALE ONLY)	F				[66-75-1]	$162
1706701	Urea C 13 (100 mg)	F0C078				[58069-82-2]	$189
1707806	Ursodiol (125 mg)	G			F-1 (11/01) F (09/99)	[128-13-2]	$129
1707908	Valerenic Acid (15 mg)	H0D126	1.00 mg/mg (ai)		G0B146 (05/05) F (01/04)	[3569-10-6]	$724
1708503	L-Valine (200 mg)	F-2			F-1 (05/02)	[72-18-4]	$162
1708707	Valproic Acid (500 mg)	K0D224	0.999 mg/mg (ai)		J1B127 (08/05) J (01/04) I-1 (11/00)	[99-66-1]	$162
1708729	Valproic Acid Related Compound A (0.25 mL) (diallylacetic acid)	F2C386			F1B156 (05/05) F (01/03)	[99-67-2]	$506
1708762	Valsartan (350 mg)	F0C147	0.995 mg/mg (an)			[137862-53-4]	$162
1708773	Valsartan Related Compound A (20 mg) ((R)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)-biphenyl-4-yl]-methyl)-valine)	F0C215				n/f	$649
1708795	Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)biphenyl-4-yl]-methyl)valine benzyl ester)	F1D025	0.99 mg/mg (ai)		F0C208 (09/05)	n/f	$649
1709007	Vancomycin Hydrochloride (4 vials, each vial contains 100,500 mcg of vancomycin activity)	L1D039			L (07/05) K (08/01)	[1404-93-9]	$162
1710006	Vanillin (200 mg)	J0A021			I (03/05) H (04/99)	[121-33-5]	$162
1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)	J1C303			J (06/05) I-1 (03/03) I (11/00)	[121-33-5]	$96
1711155	Vecuronium Bromide (50 mg)	F0C367				[50700-72-6]	$162
1711166	Vecuronium Bromide Related Compound A (25 mg) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan)	F0B178				n/f	$506
1711202	Verapamil Hydrochloride (200 mg)	G			F-4 (06/00)	[152-11-4]	$162
1711304	Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile mono-Hydrochloride)	H			G (01/01)	n/f	$506
1711406	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]	$506
1711461	Verteporfin (200 mg)	F0C166				[129497-78-5]	$162
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				n/f	$506

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1711508	Vidarabine (200 mg)	G-2	939 ug/mg (ai)		G-1 (09/05)	[24356-66-9]	$162
1713004	Vinblastine Sulfate (50 mg)	M0B308			L (12/04) K (05/99)	[143-67-9]	$368
1714007	Vincristine Sulfate (50 mg/ampule)	O0B062			N (01/03) M (04/99)	[2068-78-2]	$498
1714506	Vinorelbine Tartrate (200 mg)	F0C243				[125317-39-7]	$162
1714528	Vinorelbine Related Compound A (25 mg) (4-O-Deacetylvinorelbine tartrate)	F0C242				n/f	$506
1715000	Viomycin Sulfate (200 mg)	F				[37883-00-4]	$162
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)	V0C258			U (04/04)	[127-47-9]	$162
1717504	Vitamin D Assay System Suitability (1.5 g)	F				[67-97-0]	$162
1717708	Vitexin (30 mg)	F0C142				[3681-93-4]	$541
1719000	Warfarin (200 mg)	I0B305			H-2 (08/04) H-1 (11/01)	[81-81-2]	$162
1719102	Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one)	G1B111			G (01/04)	[37209-23-7]	$162
1720000	Xanthanoic Acid (100 mg)	G-1			G (12/00)	[82-07-5]	$506
1720203	Xanthone (100 mg)	F-1				[90-47-1]	$506
1720407	Xylazine (200 mg)	F1C001			F (02/05)	[7361-61-7]	$162
1720429	Xylazine Hydrochloride (200 mg)	F				[23076-35-9]	$162
1720600	Xylitol (1 g)	G0B037			F-3 (11/02) F-2 (05/00)	[87-99-0]	$162
1721002	Xylometazoline Hydrochloride (125 mg)	I0B101			H-1 (05/03)	[1218-35-5]	$129
1722005	Xylose (1 g)	F				[58-86-6]	$162
1724000	Yohimbine Hydrochloride (200 mg)	F				[65-19-0]	$162
1724306	Zalcitabine (200 mg)	F				[7481-89-2]	$162
1724317	Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine)	F0B234				[7481-88-1]	$506
1724500	Zidovudine (400 mg)				G (10/05) F (09/01)	[30516-87-1]	$162
1724521	Zidovudine Related Compound B (25 mg) (3'-chloro-3'-deoxythymidine)	G0B116			F-1 (03/03) F (06/01)	[25526-94-7]	$506
1724532	Zidovudine Related Compound C (100 mg) (thymine)	F-1			F (09/01)	[65-71-4]	$506
1724656	Zileuton (150 mg)	F0C062				[111406-87-2]	$162
1724667	Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea)	F0B316				n/f	$506
1724678	Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene)	F0B313				n/f	$506
1724689	Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone)	F0B299				n/f	$506
1724747	Zinc Oxide (2 g) (AS)	F0D170	99.7% (ig)			[1314-13-2]	$162
1724769	Zinc Sulfate (1 g) (AS)	F0D133	56.4% (ai)			[7446-20-2]	$162
1724805	Zolazepam Hydrochloride (500 mg)	G0C023			F-1 (03/04) F (05/02)	[33754-49-3]	$162

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
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)
1008002	alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methyl-butane	1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)
02200-3	3-Amino-4-carboxamidopyrazole Hemisulfate (50 mg) **(Limit Test)**	1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)
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)
1023403	3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg)	1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)
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)
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)
02240-6	2-Amino-4-chlorophenol (50 mg) **(Limit Test)**	1130527	Chlorzoxazone Related Compound A (25 mg) (2-Amino-4-chlorophenol)
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)
02490-5	2-Amino-2',5-dichlorobenzophenone (25 mg) **(Limit Test)**	1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)
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)
02620-8	alpha-Aminopropiophenone Hydrochloride (50 mg) **(Limit Test)**	1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)
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)
07350-3	2-(4-Biphenylyl)propionic Acid (100 mg) **(Limit Test)**	1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)
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-triiodoisophthalamide)
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-hydroxypiperidino]-butyrophenone
08650-5	Calcium Formyltetrahydrofolate (50 mg) (AS) (For Qualitiative Use Only)	1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)
11230-0	p-Chlorobenzhydrylpiperazine (25 mg)	1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)
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)
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)
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)
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)
11550-1	2-Chloro-3,5-dimethyl-phenol (50 mg) **(Limit Test)**	1122722	Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol)
11650-4	(o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test)	1141024	Clotrimazole Related Compound A (25 mg) ((o-Chlorophenyl)diphenyl-methanol)
11670-8	4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) **(Limit Test)**	1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
11900-3	4-Chloro-5-sulfamoylanthranilic Acid (100 mg) **(Limit Test)**	1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)
1119309	4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid (100 mg)	1119309	Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)
1153001	Cyclizine (1 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (04/04)
15870-8	Cyclosporine U (25 mg) **DISCONTINUED**	1158650	Cyclosporine Resolution Mixture (25 mg) (Replaces Cat. No. 15870-8 Cyclosporine U (25 mg))
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)
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)
1269006	Evans Blue (200 mg)	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (04/04)
1277208	Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) (180 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (01/04)
1286209	4-Formylbenzenesulfonamide (50 mg)	1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)
1294003	Glucagon (25 mg, 0.95 U/mg) **DISCONTINUED**		DISCONTINUED, Last Lot/Valid Use Date: H (01/05)
32720-4	3-Hydroxy-1-methylquinuclidinium Bromide (250 mg) **(Limit Test)**	1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)
1329505	9-Hydroxypropantheline Bromide (50 mg)	1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)
1330005	Hydroxypropyl Methylcellulose (250 mg)	1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)
33010-7	Hydroxypropyl Methylcellulose Phthalate (100 mg)	1335304	Hypromellose Phthalate (100 mg)
1359007	Levallorphan Tartrate (200 mg) **DISCONTINUED**		DISCONTINUED, Last Lot/Valid Use Date: G-1 (09/04)
1362001	Levo-alpha-acetylmethadol Hydrochloride **CII** (25 mg) (AS) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03)
	Melting Point Standard - Acetanilide (500 mg; approximately 114 degrees)	1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)
	Melting Point Standard - Caffeine (1 g; approximately 236 degrees)	1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)
	Melting Point Standard - Phenacetin (500 mg; approximately 135 degrees)	1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)
	Melting Point Standard - Sulfanilamide (1 g; approximately 165 degrees)	1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)
	Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees)	1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)
	Melting Point Standard - Vanillin (1 g; approximately 82 degrees)	1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)
1420006	3-Methoxytyrosine (50 mg)	1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)
42420-0	2-Methylamino-5-chlorobenzophenone (25 mg) **(Limit Test)**	1185020	Diazepam Related Compound A (25 mg) (2-Methylamino-5-chlorobenzophenone)
42430-2	3-O-Methylcarbidopa (50 mg)	1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)
1434000	Methylphenidate Hydrochloride Erythro Isomer **CII** (25 mg) **DISCONTINUED**; please order 1434011	1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)
1445222	Mitoxantrone Related Compound A Hydrochloride (30 mg) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) **DISCONTINUED**; Please order 1445211	1445211	Mitoxantrone System Suitability Mixture (0.3 mg)
46600-7	5-Nitro-2-furfuraldazine (500mg)	1466007	Nitrofurazone Related Compound A (500mg) (5-Nitro-2-furfuraldazine)
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)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
1477900	Octyl Methoxycinnamate (500 mg)	1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)
49400-2	Pancreatin (2 g)	1494057 and/or 1494079	Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g)
1527000	Phenprocoumon (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04)
53180-1	Phenylcyclohexylglycolic Acid (100 mg) **(Limit Test)**	1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)
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)
54500-1	Plastic, Negative Control	1546707	Polyethylene, High Density (3 strips)
61500-5	Sodium Taurocholate (20 g)	1071304	Bile Salts (10 g) (Sodium Taurocholate)
1653106	Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) **DISCONTINUED**		DISCONTINUED, Last Lot/Valid Use Date: F-1 (11/04)
1667279	Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) **DISCONTINUED**		DISCONTINUED, Last Lot/Valid Use Date: F (10/04)
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)
	Vitamin B1 Hydrochloride	1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)
	Vitamin B2	1603006	Riboflavin (500 mg) (Vitamin B2)
	Vitamin B3	1462006	Niacinamide (500 mg) (Vitamin B3)
	Vitamin B5	1087009	Calcium Pantothenate (200 mg) (Vitamin B5)
	Vitamin B6	1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)
	Vitamin B12	1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)
	Vitamim Bc	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)
	Vitamin C	1043003	Ascorbic Acid (1 g) (Vitamin C)
	Vitamin D2	1239005	Ergocalciferol (150 mg; 30 mg/ampule; 5 ampules) (Vitamin D2)
	Vitamin D3	1131009	Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3)
	Vitamin E Alcohol	1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)
	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)
	Vitamin K1	1538006	Phytonadione (500 mg) (Vitamin K1)
	Vitamin K3	1381006	Menadione (200 mg) (Vitamin K3)
	Vitamin M	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
Catalog Number	Description	Current Lot	Price
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	$162
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	$162
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	$162
1042000	Aprobarbital **CIII** (200 mg) (AS)	F-1	$215
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$215
1076341	Boric Acid (1 g) (AS)	F0D036	$208
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	$162
1086334	Calcium Acetate (1 g) (AS)	F0D156	$162
1086403	Calcium Carbonate (1 g) (AS)	F0D099	$162
1086436	Calcium Chloride (1 g) (AS)	F0D153	$162
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	$162
1087359	Calcium Stearate (2 g) (AS)	F0D255	$162
1087406	Calcium Sulfate (1 g) (AS)	F0D236	$162
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$506
1090003	Cannabinol **CI** (25 mg) (AS)		$215
1133503	Cholic Acid (2 g) (AS)	F3B159	$162
1148806	Corn Oil (1 g) (AS)	F0D181	$162
1150207	Cottonseed Oil (1 g) (AS)	F0D173	$162
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J	$215
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	$162
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F	$162
1251000	Estradiol Benzoate (250 mg) (AS)	G-1	$162
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	$162
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$215
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	$162
1356950	Lauroyl Polyoxylglycerides (500 mg) (AS)	F0D020	$162
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I	$562
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	$162
1374248	Magnesium Chloride (1 g) (AS)	F0D157	$162
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	$162
1374340	Magnesium Stearate (5 g) (AS)	F0D214	$162
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	$162
1375127	Manganese Chloride (1 g) (AS)	F0D150	$162
1375149	Manganese Sulfate (1 g) (AS)	F0D151	$162
1410002	Methicillin Sodium (500 mg) (AS)	J0C333	$162
1424506	Methylcellulose (1 g) (AS)	G0B222	$162
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F	$215
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1	$215
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$215
1478254	Olive Oil (1 g) (AS)	F0D175	$162
1492040	Palm Oil (1 g) (AS)	F0D179	$162
1500557	Peanut Oil (1 g) (AS)	F0D171	$162
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$215
1525707	Phenothiazine (500 mg) (AS)	F0D231	$162
1547925	Polysorbate 20 (2 g) (AS)	F0D130	$162
1547936	Polysorbate 40 (2 g) (AS)	F0D204	$162
1547947	Polysorbate 60 (2 g) (AS)	F0D131	$162
1547969	Polysorbate 80 (2 g) (AS)	F0D132	$162

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1548101	Potassium Benzoate (1 g) (AS)	F0D161	$162
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	$162
1548167	Potassium Carbonate (1 g) (AS)	F0D075	$162
1548190	Potassium Chloride (1 g) (AS)	F0D127	$162
1548280	Potassium Iodide (1 g) (AS)	F0D078	$162
1548407	Potassium Sorbate (1 g) (AS)	F0D264	$162
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	$162
1613407	Sodium Acetate (1 g) (AS)	F0D083	$162
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	$162
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	$162
1613804	Sodium Chloride (1 g) (AS)	F0D269	$162
1613859	Sodium Citrate (1 g) (AS)	F0D172	$162
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	$162
1614454	Sodium Nitrite (1 g) (AS)	F0D117	$162
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	$162
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	$162
1667585	Titanium Dioxide (1 g) (AS)	F0D079	$162
1724747	Zinc Oxide (2 g) (AS)	F0D170	$162
1724769	Zinc Sulfate (1 g) (AS)	F0D133	$162

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
AMINO ACIDS			
1012509	L-Alanine (200 mg)	F-2	$162
1021000	Aminocaproic Acid (200 mg)	G0D101	$162
1042500	L-Arginine (200 mg)	G-1	$162
1042601	Arginine Hydrochloride (125 mg)	G0B060	$129
1161509	L-Cysteine Hydrochloride (200 mg)	H	$162
1294976	Glutamic Acid (200 mg)	F0C069	$162
1294808	Glutamine (100 mg)	F0B244	$162
1295800	Glycine (200 mg)	F-3	$162
1308505	L-Histidine (200 mg)	G0A018	$162
1349502	L-Isoleucine (200 mg)	F-2	$162
1357001	L-Leucine (200 mg)	H0B237	$162
1359903	Levocarnitine (400 mg)	G0B197	$162
1359925	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1	$506
1371501	L-Lysine Acetate (200 mg)	F1C027	$162
1372005	L-Lysine Hydrochloride (200 mg)	H	$162
1411504	L-Methionine (200 mg)	G	$162
1530503	L-Phenylalanine (200 mg)	H	$162
1568506	L-Proline (200 mg)	G0D146	$162
1612506	L-Serine (200 mg)	G	$162
1667202	L-Threonine (200 mg)	G	$162
1700501	L-Tryptophan (200 mg)	G-1	$162
1705006	L-Tyrosine (500 mg)	K0C141	$162
1708503	L-Valine (200 mg)	F-2	$162
BOTANICALS			
BLACK COHOSH			
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086	$541
CAPSAICIN/CAPSICUM			
1091108	Capsaicin (100 mg)	G2D136	$162
1200600	Dihydrocapsaicin (25 mg)	G0C071	$270
CHAMOMILE			
1040708	Apigenin-7-Glucoside (30 mg)	F	$506
CHASTE TREE			
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406	$541
CRANBERRY LIQUID			
1134368	Citric Acid (200 mg)	F1B092	$162
1181302	Dextrose (500 mg)	J-1	$129
1286504	Fructose (125 mg)	I-2	$129
1374601	Malic Acid (200 mg)	G0B158	$162
1594506	Quinic Acid (200 mg)	F	$162
1617000	Sorbitol (125 mg)	H1B139	$129
1623637	Sucrose (100 mg)	H1C223	$162
ELEUTHERO			
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291	$541
ECHINACEA			
1115545	Chlorogenic Acid (50 mg)	F0C420	$162
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018	$541
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019	$541
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	$562

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FEVERFEW			
1500400	Parthenolide (25 mg)	F	$162
1606503	Rutin (100 mg)	G0C355	$162
GARLIC			
1012145	Agigenin (25 mg)	F	$506
1012950	Alliin (25 mg)	F	$1,586
1115556	beta-Chlorogenin (20 mg)	F	$506
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F	$702
1411504	L-Methionine (200 mg)	G	$162
GARLIC FLUID EXTRACT			
1013057	S-Allyl-L-Cysteine (25 mg)	F	$506
GINGER			
1091108	Capsaicin (100 mg)	G2D136	$162
1291504	Powdered Ginger (500 mg)	F	$270
GINKGO			
1115545	Chlorogenic Acid (50 mg)	F0C420	$162
1592409	Quercetin (500 mg)	F0B015	$162
1606503	Rutin (100 mg)	G0C355	$162
AMERICAN GINSENG			
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$541
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1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$541
HAWTHORN LEAF WITH FLOWER			
1115545	Chlorogenic Acid (50 mg)	F0C420	$162
1335202	Hyperoside (50 mg)	F	$889
1592409	Quercetin (500 mg)	F0B015	$162
1606503	Rutin (100 mg)	G0C355	$162
1717708	Vitexin (30 mg)	F0C142	$541
KAVA			
1355709	Powdered Kava Extract (1 g)	F0C161	$270
KAWAIN			
1355753	Kawain (200 mg)	F0C160	$216
LICORICE			
1295888	Glycyrrhizic Acid (25 mg)	F0C006	$506
MILK THISTLE			
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321	$270
1612630	Silybin (50 mg)	F	$162
1612641	Silydianin (20 mg)	F	$162
RED CLOVER			
1286060	Formononetin (50 mg)	F0C196	$541
1599500	Powdered Red Clover Extract (500 mg)	F0C188	$270
SAW PALMETTO			
1424233	Methyl Caprate (300 mg)	F	$162
1424244	Methyl Caproate (300 mg)	F	$162
1424255	Methyl Caprylate (300 mg)	G0D064	$162
1430305	Methyl Laurate (500 mg)	G0C356	$162
1430327	Methyl Linoleate (5 x 50 mg)	F	$162
1430349	Methyl Linolenate (5 x 50 mg)	F	$162
1431501	Methyl Myristate (300 mg)	G0C357	$162

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1431556	Methyl Oleate (500 mg)	G0C148	$162
1431603	Methyl Palmitate (300 mg)	F	$162
1431625	Methyl Palmitoleate (300 mg)	F	$162
1437508	Methyl Stearate (300 mg)	F	$162
ST. JOHN S WORT			
1115545	Chlorogenic Acid (50 mg)	F0C420	$162
1335202	Hyperoside (50 mg)	F	$889
1485001	Oxybenzone (150 mg)	H0B263	$162
1606503	Rutin (100 mg)	G0C355	$162
VALERIAN			
1707908	Valerenic Acid (15 mg)	H0D126	$724
MISCELLANEOUS DIETARY SUPPLEMENTS			
1133570	Chondroitin Sulfate Sodium (300 mg)	F0B256	$162
1133638	Chromium Picolinate (100 mg)	F	$162
1150353	Creatinine (100 mg)	F	$162
1294207	Glucosamine Hydrochloride (200 mg)	F0C363	$162
1611955	Selenomethionine (100 mg)	F0B006	$162
VITAMINS-MINERALS			
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012	$162
1071508	Biotin (200 mg)	H1B019	$162
1086356	Calcium Ascorbate (200 mg)	F-1	$162
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	$162
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157	$165
1131803	Delta-4,6-cholestadienol (30 mg)	F	$506
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N	$162
1179504	Dexpanthenol (500 mg)	J0C293	$166
1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275	$175
1241007	Ergosterol (50 mg)	H	$162
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P	$162
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176	$162
1381006	Menadione (200 mg) (Vitamin K3)	H-3	$162
1461003	Niacin (200 mg)	H2C121	$162
1462006	Niacinamide (500 mg) (Vitamin B3)	M-1	$162
1494501	Panthenol, Racemic (200 mg)	G	$162
1494807	Pantolactone (500 mg)	F	$506
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303	$162
1550001	Potassium Gluconate (200 mg)	H0C064	$162
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P	$162
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021	$162
1613509	Sodium Ascorbate (200 mg)	G2C067	$162
1614002	Sodium Fluoride (1 g) (FOR U.S. SALE ONLY)	H-1	$162
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O	$162
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M	$162
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K	$162
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)		$162
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)	V0C258	$162
1717504	Vitamin D Assay System Suitability (1.5 g)	F	$162

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1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016	$215
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F	$215
1015008	Alprazolam **CIV** (200 mg)	H1C133	$215
1030001	Amobarbital **CII** (200 mg)	F-2	$215
1036008	Anileridine Hydrochloride **CII** (250 mg)	F	$215
1042000	Aprobarbital **CIII** (200 mg) (AS)	F-1	$215
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$215
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	F-1	$215
1079000	Butabarbital **CIII** (200 mg)	H0C007	$215
1081002	Butalbital **CIII** (200 mg)	H0C054	$215
1082504	Butorphanol Tartrate **CIV** (500 mg)	J	$215
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$506
1090003	Cannabinol **CI** (25 mg) (AS)		$215
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I	$582
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063	$215
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4	$215
1140305	Clonazepam **CIV** (200 mg)	G1B175	$215
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027	$215
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074	$215
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034	$215
1144000	Codeine Phosphate **CII** (100 mg)	J0C200	$215
1145003	Codeine Sulfate **CII** (250 mg)	H-2	$215
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	$225
1183002	Diacetylmorphine Hydrochloride (Heroin Hydrochloride) **CI** (25 mg) (AS)	J	$215
1185008	Diazepam **CIV** (100 mg)	I	$215
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010	$215
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H	$215
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	$215
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I	$215
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011	$215
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264	$250
1280009	Fluoxymesterone **CIII** (200 mg)	G-2	$215
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	$215
1295006	Glutethimide **CII** (500 mg)	F	$215
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$215
1307003	Hexobarbital **CIII** (500 mg)	F	$215
1315001	Hydrocodone Bitartrate **CII** (250 mg)	K0C217	$215
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214	$534
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372	$215
1356009	Ketamine Hydrochloride **CIII** (250 mg)	G-2	$215
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	$215
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	$215
1370305	Lorazepam **CIV** (200 mg)	I0C048	$215
1371002	Lysergic Acid Diethylamide Tartrate (LSD) **CI** (10 mg) (AS)	I	$562
1375309	Mazindol **CIV** (350 mg)	H	$215
1383001	Meperidine Hydrochloride **CII** (200 mg)	I	$215
1386000	Mephobarbital **CIV** (250 mg)	G	$215
1389008	Meprobamate **CIV** (200 mg)	G-1	$215
1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163	$215

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Cat. No.	Description	Curr. Lot	Price
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I	$215
1404000	Methaqualone **CI** (500 mg)	F-1	$215
1405002	Metharbital **CIII** (200 mg)	F-2	$215
1413000	Methohexital **CIV** (500 mg)	G0D252	$215
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) **CI** (25 mg) (AS)	F	$215
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) **CI** (25 mg) (AS)	F-1	$215
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241	$172
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	$582
1438001	Methyltestosterone **CIII** (200 mg)	J	$215
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$215
1448005	Morphine Sulfate **CII** (500 mg)	M0D016	$345
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I	$215
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone hydrochloride)	F	$506
1454008	Nandrolone **CIII** (50 mg)	F4D144	$582
1455000	Nandrolone Decanoate **CIII** (250 mg)	I	$215
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H	$215
1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035	$582
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177	$582
1482003	Oxandrolone **CIII** (50 mg)	G0B220	$215
1483006	Oxazepam **CIV** (200 mg)	H0D259	$215
1485191	Oxycodone **CII** (200 mg)	I1D206	$215
1487007	Oxymetholone **CIII** (200 mg)	G1B247	$215
1488000	Oxymorphone **CII** (500 mg)	H0B214	$215
1505007	Pentazocine **CIV** (500 mg)	I0C418	$215
1507002	Pentobarbital **CII** (200 mg)		$215
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$215
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G	$215
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2	$215
1524001	Phenobarbital **CIV** (200 mg)	J	$215
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309	$215
1554501	Prazepam **CIV** (500 mg)	G0C066	$215
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285	$215
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	$215
1592205	Quazepam **CIV** (200 mg)	F	$215
1611004	Secobarbital **CII** (200 mg)	H	$215
1620005	Stanozolol **CIII** (200 mg)	F-3	$215
1623648	Sufentanil Citrate **CII** (25 mg)	H0B208	$229
1643000	Talbutal **CIII** (250 mg)	F	$215
1643408	Temazepam **CIV** (200 mg)	H0C205	$215
1645006	Testolactone **CIII** (125 mg)	F-1	$172
1646009	Testosterone **CIII** (125 mg)	I1B253	$172
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	$215
1648004	Testosterone Enanthate **CIII** (200 mg)	J	$215
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005	$215
1656308	Thiamylal **CIII** (200 mg)	F	$215
1661002	Thiopental **CIII** (250 mg)	I1D198	$215
1680506	Triazolam **CIV** (200 mg)	H0B041	$215

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USP–NF (*Print or Electronic*)

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 _____

Address _____

_____

_____

Telephone No. ( ) _____
(area code)

*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*

January–February 2005

GABAPENTIN

DSD Mgh #34587

PF	LGS#	Reagent Brand	Type of Test	Comments
31(1)	L1	Luna C18	Assay and Related Compounds	Test 1, Method 1 and Method 2: 25 cm x 4.6 mm, 5 µm, manufacturer Phenomenex.
31(1)	L7	Symmetry C8	Related compounds	Test 2: 25 cm x 4.6 mm, 5 µm, manufacturer Waters Corp.

ISOMALT

DSD Mgh #781

PF	LGS#	Reagent Brand	Type of Test	Comments
31(1)	L19	Aminex Carbohydrate HPX-87	Assay and Related Compounds	Analytical column 7.8 mm x 30 cm, guard column 4.6 mm x 3 cm, manufacturer BioRad.

OXANDROLONE TABLETS

DSD Mgh #59140

PF	LGS#	Reagent Brand	Type of Test	Comments
31(1)	G27	Rtx-5 Amine	Dissolution	0.53 mm x 30 m, 0.5 µm, manufacturer Restek.

TIAMULIN

DSD Mgh #1136

PF	LGS#	Reagent Brand	Type of Test	Comments
31(1)	G16	HP-INNOWax	Limit of	Limit of alcohol and toluene. 0.53 mm x 30 m, 1.0 µm film, manufacturer Agilent.
31(1)	L1	Supelcosil LC-18-DB	Assay and Related Compounds	4.6 mm x 15 cm, 5 µm, manufacturer Supelco. Alternative column Polaris C18-A, same dimensions, manufacturer Metachem Technologies.

Filename:	PF311Chrom Reagents.doc
Directory:	G:\PF\Production\ChromReagents
Template:	C:\Documents and Settings\dm\Application Data\Microsoft\Templates\Normal.dot
Title:	Chromatographic Reagents Used in USP̃NF and
Subject:	
Author:	USP
Keywords:	
Comments:	
Creation Date:	11/29/2004 2:19 PM
Change Number:	4
Last Saved On:	11/29/2004 2:40 PM
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PHARMACOPEIAL FORUM VOL. 31 NO. 2 MAR.–APR. 2005

* The *USP–NF* (*USP29–NF24*), 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:

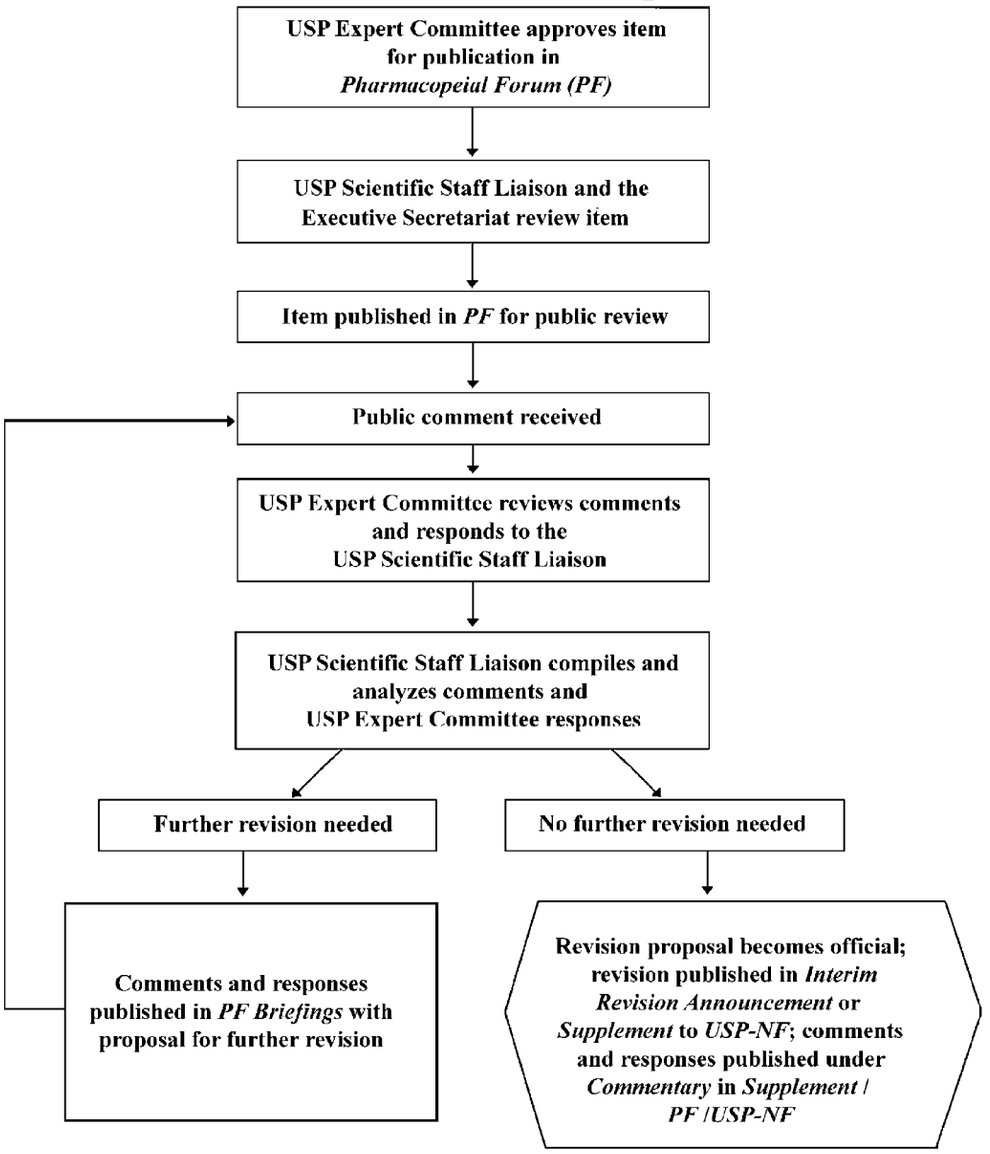
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official 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* 31(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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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 7a—Antibiotics; 7b—Antimicrobials and Antivirals
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.

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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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.

In Memoriam

Charles H. Barnstein, Ph.D.

With great sadness USP notes the death of Charles H. Barnstein, Ph.D. Charlie served more than 35 years as a USP staff member. His name is synonymous with the highest standards of USP because for years he was involved directly in the publication of the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*), *Pharmacopeial Forum,* and the *USP Dictionary of Drug Names* and was involved with the United States Adopted Names (USAN) Council for many years. Dr. Barnstein served as a respected mentor to several generations of USP staff, imparting his scientific and technical knowledge and his rigorous editorial expertise to the development and production of USP publications. He was a member of the *National Formulary* (*NF*) staff at the American Pharmaceutical Association (now American Pharmacists Association). When the *NF* was purchased by USP in 1975, he joined USP staff. Dr. Barnstein officially retired from USP in 2000, but USP retained his invaluable expertise as a consultant in the area of nomenclature and labeling, and he continued to serve as a USP observer on the USAN Council. His dedication to *USP–NF,* to the Committee of Revision/Council of Experts, and to the Expert Committees was exemplary and serves as a model for anyone involved with USP. His passing leaves a void that will be very difficult to fill.

ADVANCE NOTICE OF UPCOMING OFFICIAL REVISIONS TO THE *USP–NF.* In order to provide as much time as possible for industry to adopt revisions made to the compendia, upcoming official revisions to the *USP–NF* are now being announced on the USP website as soon as they are voted on to become official by the appropriate Expert Committees of the Council of Experts. Readers are directed to the "Notices" section found in the top right corner of the USP homepage at www.usp.org. By clicking on "Upcoming Official Revisions to the *USP–NF:* Reference Standards Required But Not Available" you are taken to a page where upcoming revisions to the compendia are listed. The information posted includes the title of the item being revised, the *PF* citation where the revision was proposed, and a description of the proposal. In addition, an e-mail link to the USP Scientific Liaison for each revision is listed in parentheses after the item. The actual content and official date of each revision will be published in either an annual edition, *Supplement,* or *Interim Revision Announcement* and the items are sorted according to the publication in which they are to appear.

In addition, readers will also find a list of new USP Reference Standards that correspond to new *USP–NF* monographs but unfortunately are not yet available. The official dates of any *USP–NF* Standards, tests, or assays that require the use of these Standards are postponed until further notice pending availability of the Standards.

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 Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@usp.org, 301-816-8530; or visit the website at www.usp.org/education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2005

Date	Name of Course	Location
March 15	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
March 16	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
April 11	Basic Statistics and Their Practical Applications to the USP	USP Headquarters, Rockville, MD
May 18	Analytical Method Validation	USP Headquarters, Rockville, MD
July 18 and 19	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
August 12	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
August 17	Analytical Method Validation	USP Headquarters, Rockville, MD
August 18	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
August 19	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
October 19 and 20	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 7	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 8	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	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.

Publication and Comment Schedule for *USP 28–NF 23*

Publication	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

Publication and Comment Schedule for *USP 29–NF 24*

Publication	Comment Deadline	Publication Date	Official Date
Main Book	May 15, 2005	November 2005	January 2006
Supplement One	October 15, 2005	February 2006	April 2006
Supplement Two	February 17, 2006	June 2006	August 2006

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. 2005	Apr. 1, 2005
PF 31(2) [Mar.–Apr. 2005]	Mar. 2005	Not Applicable
2nd IRA [published in *PF* 31(2)]	Mar. 2005	Apr. 1, 2005
PF 31(3) [May–June 2005]	May 2005*	Not Applicable
3rd IRA [published in *PF* 31(3)]	May 2005*	June 1, 2005*
2nd Supplement	June 2005*	Aug. 1, 2005*
PF 31(4) [July–Aug. 2005]	July 2005*	Not Applicable
4th IRA [published in *PF* 31(4)]	July 2005*	Aug. 1, 2005*
PF 31(5) [Sept.–Oct. 2005]	Sept. 2005*	Not Applicable
5th IRA [published in *PF* 31(5)]	Sept. 2005*	Oct. 1, 2005*
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005*	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005*	Dec. 1, 2005*

* 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 (*USP27*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 27*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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.

Pharmacopeial Forum
Vol. 31(2) [Mar.–Apr. 2005]

SECOND INTERIM REVISION ANNOUNCEMENT to *USP 28* and to *NF 23*

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 April 1, 2005. **Released March 1, 2005.**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of *USF–NF* users.

USP Adipic Acid RS (September 1, 2005)
USP Alcohol RS (May 1, 2005)
USP Alcohol Determination–Acetonitrile RS (March 1, 2005)
USP Alcohol Determination–Alcohol RS (March 1, 2005)
USP Aluminum Sulfate (AS)
USP Amiodarone Hydrochloride RS (July 1, 2005)
USP Amlodipine Besylate RS (May 1, 2005)
USP Ammonium Carbonate (AS)
USP Ammonium Phosphate Dibasic (AS)
USP Ascorbyl Palmitate RS (September 1, 2005)
USP Bismuth Subcarbonate RS (September 1, 2005)
USP Bismuth Subgallate RS (September 1, 2005)
USP Boric Acid (AS)
USP Butylated Hydroxytoluene RS (March 1, 2005)
USP Calcium Acetate (AS)
USP Calcium Carbonate (AS)
USP Calcium Chloride (AS)
USP Calcium Hydroxide (AS)
USP Calcium Stearate (AS)
USP Calcium Sulfate (AS)
USP Candelilla Wax RS (March 1, 2005)
USP Caprylocaproyl Polyoxylglycerides RS (March 1, 2005)
USP Carboxymethylcellulose Sodium RS (September 1, 2005)
USP Carprofen RS (September 1, 2005)
USP Cellaburate (cellulose acetate butyrate) RS (May 1, 2005)
USP Powdered Black Cohosh Extract RS (March 1, 2005)
USP Corn Oil (AS)
USP Cottonseed Oil (AS)
USP Dehydrated Alcohol RS (May 1, 2005)
USP Dextran 1 RS (July 1, 2005)
USP Dextran T-10 RS (July 1, 2005)
USP Dibutyl Phthalate RS (March 1, 2005)
USP Dibutyl Sebacate (AS)
USP Dichlorvos (AS)
USP Ferrous Sulfate (AS)
USP Fexofenadine Hydrochloride RS (July 1, 2005)
USP Fexofenadine Related Compound A RS (July 1, 2005)
USP Fexofenadine Related Compound B RS (July 1, 2005)
USP Fluconazole RS (July 1, 2005)
USP Fluconazole Related Compound A RS (July 1, 2005)
USP Fluconazole Related Compound B RS (July 1, 2005)
USP Fluconazole Related Compound C RS (July 1, 2005)
USP Fludeoxyglucose Related Compound A RS (September 1, 2005)
USP Gemcitabine Hydrochloride RS (March 1, 2005)
USP Glacial Acetic Acid (AS)
USP Hypromellose Acetate Succinate RS (July 1, 2005)
USP Indinavir RS (September 1, 2005)
USP Indinavir System Suitability RS (September 1, 2005)
USP Isopropyl Alcohol RS (September 1, 2005)
USP Lactase RS (May 1, 2005)
USP Lactic Acid (AS)
USP Lauroyl Polyoxylglycerides (AS)
USP Loratadine Related Compound A RS (May 1, 2005)
USP Loratadine Related Compound B RS (May 1, 2005)
USP Losartan Potassium RS (July 1, 2005)
USP Lutein RS (September 1, 2005)
USP Magnesium Carbonate (AS)
USP Magnesium Chloride (AS)
USP Magnesium Hydroxide (AS)
USP Magnesium Stearate (AS)
USP Magnesium Sulfate (AS)
USP Mangafodipir Related Compound A RS (July 1, 2005)
USP Mangafodipir Related Compound B RS (July 1, 2005)
USP Mangafodipir Trisodium RS (July 1, 2005)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Meglumine RS (September 1, 2005)
USP Melengestrol Acetate RS (September 1, 2005)
USP Melengestrol Acetate Related Compound A RS (September 1, 2005)
USP Melengestrol Acetate Related Compound B RS (September 1, 2005)
USP Methyl Salicylate RS (September 1, 2005)
USP Mirtazapine RS (March 1, 2005)
USP Monobasic Potassium Phosphate (AS)
USP Monosodium Glutamate RS (September 1, 2005)
USP Morantel Tartrate RS (September 1, 2005)
USP Nabumetone Related Compound A RS (May 1, 2005)
USP Nevirapine Anhydrous RS (March 1, 2005)
USP Olive Oil (AS)
USP Omeprazole Related Compound A RS (September 1, 2005)
USP Ondansetron Resolution Mixture RS (May 1, 2005)
USP Palm Oil (AS)
USP Pancuronium Bromide RS (September 1, 2005)
USP Paroxetine Related Compound F RS (May 1, 2005)
USP Paroxetine Related Compound G RS (May 1, 2005)
USP Peanut Oil (AS)
USP Phenothiazine (AS)
USP Phenoxyethanol RS (July 1, 2005)
USP Phosphoric Acid (AS)
USP Polysorbate 20 (AS)
USP Polysorbate 40 (AS)
USP Polysorbate 60 (AS)
USP Polysorbate 80 (AS)
USP Potassium Benzoate (AS)
USP Potassium Bitartrate (AS)
USP Potassium Carbonate (AS)
USP Potassium Chloride (AS)
USP Potassium Citrate RS (September 1, 2005)
USP Potassium Iodide (AS)
USP Potassium Nitrate (AS)
USP Potassium Sodium Tartrate RS (September 1, 2005)
USP Potassium Sorbate (AS)
USP Propionic Acid (AS)
USP Residual Solvent Class 2—Chloroform RS (May 1, 2005)
USP Residual Solvent Class 2—Cyclohexane RS (May 1, 2005)
USP Residual Solvent Class 2—1,2-Dichloroethene RS (March 1, 2005)
USP Residual Solvent Class 2—1,2-Dimethoxyethane RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS (May 1, 2005)
USP Residual Solvent Class 2—2-Ethoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Formamide RS (May 1, 2005)
USP Residual Solvent Class 2—2-Methoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Methylbutylketone RS (May 1, 2005)
USP Residual Solvent Class 2—Methylcyclohexane RS (March 1, 2005)
USP Residual Solvent Class 2—*N*-Methylpyrrolidone RS (May 1, 2005)

USP Residual Solvent Class 2—Mixture A RS (May 1, 2005)
USP Residual Solvent Class 2—Mixture C RS (May 1, 2005)
USP Residual Solvent Class 2—Nitromethane RS (May 1, 2005)
USP Residual Solvent Class 2—Pyridine RS (May 1, 2005)
USP Residual Solvent Class 2—Sulfolane RS (May 1, 2005)
USP Residual Solvent Class 2—Tetralin RS (May 1, 2005)
USP Residual Solvent Class 2—Trichloroethylene RS (May 1, 2005)
USP Sevoflurane Related Compound B RS (July 1, 2005)
USP Sevoflurane Related Compound C RS (July 1, 2005)
USP β-Sitosterol RS (September 1, 2005)
USP Sodium Acetate (AS)
USP Sodium Bicarbonate (AS)
USP Sodium Carbonate Anhydrous (AS)
USP Sodium Chloride (AS)
USP Sodium Citrate (AS)
USP Sodium Metabisulfite (AS)
USP Sodium Nitrite (AS)
USP Sodium Sulfate Anhydrous (AS)
USP Sodium Thiosulfate (AS)
USP Sorbic Acid (AS)
USP Tannic Acid RS (September 1, 2005)
USP Tartaric Acid RS (September 1, 2005)
USP Terbutaline Related Compound A RS (September 1, 2005)
USP Titanium Dioxide (AS)
USP Tolcapone RS (July 1, 2005)
USP Tolcapone Related Compound B RS (September 1, 2005)
USP Tylosin Tartrate RS (September 1, 2005)
USP Urea RS (September 1, 2005)
USP Zinc Oxide (AS)
USP Zinc Sulfate (AS)

The official dates of any *USP 28* or *NF 23* 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 Bupropion Hydrochloride Related Compound A RS
USP Bupropion Hydrochloride Related Compound B RS
USP Bupropion Hydrochloride Related Compound C RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Bupropion Hydrochloride Related Compound F RS
USP Cinoxate RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Maltose Monohydrate RS
USP Menotropins RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Propofol RS
USP Propofol Related Compound A RS
USP Propofol Related Compound B RS
USP Propofol Resolution RS
USP Propofol for System Suitability RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Terbutaline Related Compound A RS
USP Δ^8-tetrahydrocannabinol RS
USP Δ^9-tetrahydrocannabinol RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

MONOGRAPHS (USP)

Aspirin Delayed-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method A* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

Apparatus 1: 100 rpm.
Time: 90 minutes, for *Buffer stage*.
Diluent—Prepare a mixture of 0.1 N hydrochloric acid and 0.20 M tribasic sodium phosphate (3 : 1), and adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved by determining UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid (about 280 nm in the *Acid stage*, and about 265 nm in the *Buffer stage*), using a filtered portion of the solution under test, diluted, if necessary, with 0.1 N hydrochloric acid (analyzing the *Acid stage*) and with *Diluent* (analyzing the *Buffer stage*), in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same *Medium*.

•(Official April 1, 2006)•2

Aspirin Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

Apparatus 1: 100 rpm.
Time: 90 minutes, for *Buffer stage*.
Diluent—Prepare a mixture of 0.1 N hydrochloric acid and 0.20 M tribasic sodium phosphate (3 : 1), and adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved by determining UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid (about 280 nm in the *Acid stage*, and about 265 nm in the *Buffer stage*), using a filtered portion of the solution under test, diluted, if necessary, with 0.1 N hydrochloric acid (analyzing the *Acid stage*) and with *Diluent* (analyzing the *Buffer stage*), in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same *Medium*.

•(Official April 1, 2006)•2

Aspirin Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 60 rpm.
Times: 1 hour and 4 hours.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved from UV absorbances at the isosbestic point at about 280 nm, using filtered portions of the solution under test, suitably diluted with 0.1 N hydrochloric acid, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same *Medium*.
Tolerances—The percentages of the labeled amount of $C_9H_8O_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 20% and 55%
4	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2
Medium: water; 1000 mL.
Apparatus 2: 30 rpm.
Times: 1, 2, 4, and 8 hours.
Procedure—Determine the amount of $C_9H_8O_4$ dissolved from UV absorbances at the isosbestic point at about 265 nm, using filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same *Medium*. [NOTE—Prepare the Standard solution at the time of use. An amount of alcohol not to exceed 5% of the total volume of the Standard solution may be used to bring the USP Reference Standard into solution prior to dilution with *Medium*.]
Tolerances—The percentages of the labeled amount of $C_9H_8O_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 15% and 40%
2	between 25% and 60%
4	between 35% and 75%
8	not less than 70%

•(Official April 1, 2006)•2

Bupropion Hydrochloride Extended-Release Tablets

Change to read:

■**Labeling**—When more than one •*Dissolution Test*•2 is given, the labeling states the •*Dissolution Test*•2 used only if *Test 1* is not used.■1S (*USP28*)

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

■TEST 1—■1S (*USP28*)
Medium: water; 900 mL.

Interim Revision Announcement

Apparatus 2: 50 rpm.
Times: 1, 4, and 8 hours.
Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2*.•$_2$

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

■TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2*.•$_2$
Medium: 0.1 N hydrochloric acid, pH 1.5; 900 mL.
Apparatus 1: 50 rpm.
Times: 1, 2, 4, and 6 hours.
Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.
Buffer solution—Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.
Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*
Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains 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 column efficiency is not less than 2000 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2*.•$_2$

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3*.•$_2$
Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except using the wavelength of about 250 nm.
Times: 1, 2, 4, and 6 hours.
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2*.•$_2$

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

■1S (*USP28*)

•(Official April 1, 2006)•$_2$

Carbamazepine Tablets

Change to read:

Dissolution ⟨711⟩—
FOR PRODUCTS LABELED AS 100-MG CHEWABLE TABLETS—
TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.
Medium: water containing 1% sodium lauryl sulfate; 900 mL.
Apparatus 2: 75 rpm.
Time: 60 minutes.
Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 288 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium.* [NOTE—A volume of methanol not exceeding 1% of the final total volume of the Standard solution may be used to dissolve the carbamazepine.]
Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 1*,•$_2$ with the following exceptions: at S_2, no unit is less than Q – 5%; at S_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.
TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: 0.1 N hydrochloric acid containing 1% sodium lauryl sulfate; 225 mL. Add 2 drops of simethicone to each.
Apparatus 3: ••$_2$ 35 dips per minute; use 20-mesh screen on the top of the reciprocating cylinder and a 100-mesh screen on the bottom of the reciprocating cylinder.
Time: 60 minutes.
Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.
Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes, the acceptance criteria specified for *Test 1* being used.
FOR PRODUCTS LABELED AS 200-MG TABLETS—
TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.
Times and *Tolerances:* between 45% and 75% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 2,*•$_2$ with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated

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range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances:* between 60% and 85% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 2,*•$_{\bullet 2}$ with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

•(Official April 1, 2006)•$_{\bullet 2}$

Carbamazepine Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•$_{\bullet 2}$

Medium: water; 900 mL, 1800 mL for 400-mg Tablets.

Apparatus 1: 100 rpm.

Times: 3, 6, 12, and 24 hours.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.

Tolerances—The percentages *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{\bullet 2}$

Time (hours)	Amount dissolved
3	between 10% and 35%
6	between 35% and 65%
12	between 65% and 90%
24	not less than 75%

•(Official April 1, 2006)•$_{\bullet 2}$

Cefaclor Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•$_{\bullet 2}$

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1 (10-mesh basket): 100 rpm.

Times: 30, 60, and 240 minutes.

Procedure—Quantitatively dilute filtered portions of the solution under test with 0.1 N hydrochloric acid to obtain a test solution having a concentration of cefaclor ($C_{15}H_{14}ClN_3O_4S$) estimated to be about 25 µg per mL. Determine the amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 265 nm, in comparison with a Standard solution having a similar, known concentration of USP Cefaclor RS in the same *Medium*.

Tolerances—The percentages of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$) dissolved at the times specified conform to •*Acceptance Table 2.*•$_{\bullet 2}$

Time (minutes)	Amount dissolved
30	between 5% and 30%
60	between 20% and 50%
240	not less than 80%

•(Official April 1, 2006)•$_{\bullet 2}$

Chlorpheniramine Maleate Extended-Release Capsules

Change to read:

Labeling—Label the Capsules to indicate the •*Dissolution Test*•$_{\bullet 2}$ with which the product complies.

•(Official April 1, 2006)•$_{\bullet 2}$

Change to read:

•**Dissolution** ⟨711⟩—•$_{\bullet 2}$

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•$_{\bullet 2}$

Medium: water; 500 mL.

Apparatus 1: 100 rpm.

Times: 1.5, 6.0, and 10.0 hours.

Procedure—Determine the amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved by employing the method set forth in the *Assay*, using a filtered portion of the solution under test in comparison with a Standard solution having a known concentration of USP Chlorpheniramine Maleate RS in the same medium.

Tolerances—The percentages of the labeled amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{\bullet 2}$

Time (hours)	Amount dissolved
1.5	between 15% and 40%
6.0	between 50% and 80%
10.0	not less than 70%

TEST 2— If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•$_{\bullet 2}$ Proceed as directed for *Procedure* •for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•$_{\bullet 2}$

Medium—Prepare as directed under *Method B,* except use 900 mL of media. Operate the apparatus for 1 hour in the *Acid Stage* and use the acceptance criteria given under *Tolerances*. Operate the apparatus for 6 hours in the *Buffer Stage*, except to use 900 mL of simulated intestinal fluid TS without enzyme, and use the acceptance criteria given under *Tolerances*.

Apparatus 2: 50 rpm.

Times: 1.0 hour, 3.0 hours, 7.0 hours.

Procedure—Proceed as directed in *Test 1*.

Tolerances—The percentages of the labeled amount of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1.0	between 30% and 60%
3.0	between 55% and 85%
7.0	not less than 70%

•(Official April 1, 2006)•2

Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for phenylpropanolamine hydrochloride*.
Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved at the specified times conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•2

Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for phenylpropanolamine hydrochloride*.
Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_9H_{13}NO \cdot HCl$ dissolved at the specified times conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•2

Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-Release Capsules

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.
Procedure—Determine the amounts of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for pseudoephedrine hydrochloride*, respectively.
Tolerances—The percentages of the labeled amounts of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ and $C_{10}H_{15}NO \cdot HCl$ dissolved at the specified times conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2
Medium 1: simulated gastric fluid TS, prepared without pepsin; 900 mL.
Medium 2: simulated intestinal fluid TS, prepared without pancreatin; 900 mL.
Apparatus 2: 50 rpm.
Time for Medium 1: 1.5 hours.
Times for Medium 2: 3 and 6 hours.
Procedure—Determine the amounts of chlorpheniramine maleate ($C_{16}N_{19}ClN_2 \cdot C_4H_4O_4$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by employing the methods set forth in the *Assay for chlorpheniramine maleate* and the *Assay for pseudoephedrine hydrochloride*, respectively, using Standard solutions having known concentrations of the relevant USP Reference Standard in the appropriate *Medium.*

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Tolerances—The percentages of the labeled amounts of $C_{16}N_{19}ClN_2 \cdot C_4H_4O_4$ and $C_{10}H_{15}NO \cdot HCl$ dissolved at the specified times conform to •*Acceptance Table 2*.•$_2$

Time (hours)	Amount dissolved (*Medium 1*)	Amount dissolved (*Medium 2*)
1.5	between 15% and 40%	
3.0		between 35% and 75%
6.0		not less than 50%

•(Official April 1, 2006)•$_2$

Clonidine Transdermal System

Change to read:

Drug release ⟨724⟩—

Medium: 0.001 M phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; 200 mL for systems containing more than 5 mg of clonidine.

Times: 8, 24, 96, and 168 hours.

Apparatus 7—Proceed as directed in the chapter, using the transdermal system holder-angled disk •(see *Figure 4a*).•$_2$ The appropriate size of the holder, 1.42 or 1.98 inches, 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 immersion. 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.

Mobile phase—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⟩).

System suitability solution—Prepare a solution of USP Clonidine 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 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 the beakers to cool to room temperature and make up for evaporative *Medium* losses by adding *Medium* to obtain the original weight. Mix.

* 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.

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 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 2.0; 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 25 µL) of filtered portions of each *Standard solution* and *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, in 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 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 1* under *Drug Release* ⟨724⟩.•$_2$

Time (hours)	Time for sampling (hours)	Release rate (µg/h/cm^2)
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

•(Official April 1, 2006)•$_2$

Diazepam Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•$_2$

Medium: simulated gastric fluid TS, prepared without enzymes; 900 mL.

Apparatus 1: 100 rpm.

Times: 1 hour; 4 hours; 8 hours; 12 hours.

Mobile phase—Prepare a suitable degassed and filtered mixture of methanol and water (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Buffer solution—Dissolve 77.1 g of ammonium acetate in water to make 1000 mL of solution, and adjust with ammonium hydroxide to a pH of 8.7.

Standard solution—Dissolve an accurately weighed quantity of USP Diazepam RS in *Medium*, dilute quantitatively with *Medium* to obtain a solution having a known concentration of about 0.15 mg per mL, and mix. Transfer 2.0-, 5.0-, 8.0-, and 10.0-mL aliquots of this solution to separate 100-mL volumetric flasks, add *Medium* to volume, and mix. Pipet 1.0 mL of each solution and 1.0 mL of *Buffer solution* into individual small vials, mix, and allow to stand at room temperature for about 10 minutes.

Test solution—Wrap each Capsule in a coil made from a 10-cm piece of 18-gauge copper wire weighing approximately 750 mg, so that the wire encircles the Capsule 4 times. The Capsule enclosed in the coil remains at the bottom of the basket (it should not float).

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Filter a portion of the solution under test, obtained at each time interval, through a suitable 0.6-µm porosity filter. Pipet 1.0 mL of each solution and 1.0 mL of *Buffer solution* into individual small vials, mix, and allow to stand at room temperature for about 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and an 8-mm × 10-cm column that contains packing L1. The flow rate is about 5.0 mL per minute. Chromatograph the appropriate *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not greater than 1.7; 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of $C_{16}H_{13}ClN_2O$ dissolved from peak responses of diazepam obtained from the *Test solution* and the *Standard solution*.

Tolerances—The percentage of the labeled amount of $C_{16}H_{13}ClN_2O$ dissolved is within the range stated at each of the following times.

Time (hours)	Amount dissolved
1	between 15% and 27%
4	between 49% and 66%
8	between 76% and 96%
12	between 85% and 115%

•(Official April 1, 2006)•2

Diclofenac Sodium Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2 (paddles constructed of, or coated with, polytef being used): 50 rpm.

Procedure—At the end of 2 hours, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the *Buffer stage*. To the 0.1 N hydrochloric acid remaining in each vessel, add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a second 100-mL volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900 : 20) to volume, and mix. This Standard solution contains about 13.6 µg of USP Diclofenac Sodium RS per mL.

BUFFER STAGE—

pH 6.8 Phosphate buffer—Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution. Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Medium: pH 6.8 Phosphate buffer; 900 mL.

Apparatus 2: 50 rpm.

Procedure—At the end of 45 minutes, determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with *Medium*, in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a second 100-mL volumetric flask, dilute with *Medium*, as obtained in the *Buffer stage,* to volume, and mix. This Standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{14}H_{10}Cl_2NNaO_2$ is dissolved.

•(Official April 1, 2006)•2

Diltiazem Hydrochloride Extended-Release Capsules

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2 Proceed as directed for •*Extended-Release Dosage Forms.*•2

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Times: 3, 9, and 12 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

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Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to the *Acceptance Table* given.

Time (hours)	Amount dissolved
3	between 10% and 25%
9	between 45% and 85%
12	not less than 70%

Acceptance Table

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. At 3 hours none of the units is outside the range of 10% to 35% of labeled content; at 9 hours none of the units is outside the range of 45% to 95% of labeled content; and at 12 hours none of the units is less than 65% of labeled content 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. At 3 hours not more than 2 of the 24 units are outside the range of 10% to 35% of labeled content, and these two units must be within the range of 5% to 45% of labeled content; at 9 hours not more than 2 of 24 of the units are outside the range of 45% to 95% of labeled content, and these two units must be within the range of 35% to 100% of labeled content; at 12 hours not more than 2 of the 24 units are less than 65% of labeled content at the final test time, and these two units cannot be less than 60% of labeled content at the final test time.

TEST 4—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 4.*•$_2$

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 4, 8, 12, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
4	between 10% and 25%
8	between 35% and 60%
12	between 55% and 80%
24	not less than 80%

TEST 5—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 5.*•$_2$

Medium: 0.05 M phosphate buffer, pH 7.2; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times: 1, 3, and 8 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 15%
3	between 45% and 70%
8	not less than 80%

TEST 10—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 10.*•$_2$

Medium: 0.05 M phosphate buffer, pH 6.5; 900 mL. Prepare the buffer employing the following method. Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5.

Apparatus 1: 100 rpm.

Procedure—Proceed as directed under *Test 1.*

Times: 1, 6, 9, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	not more than 10%
6	between 10% and 30%
9	between 34% and 60%
24	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 *Dissolution Test 2.*•$_2$

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 4, 10, and 15 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 70% and 90%
15	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3.*•$_2$

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 100 rpm.

Times: 6, 12, 18, 24, and 30 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 85%

TEST 6—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 6.*•2

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 4, 8, 12, and 16 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	not more than 25%
4	between 25% and 50%
8	between 60% and 85%
12	not less than 70%
16	not less than 80%

TEST 7—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 7.*•2

Medium: pH 4.2 acetate buffer; 900 mL. Prepare the buffer by employing the following method. Transfer 115 mL of acetic acid to a 10-L volumetric flask, dilute with water to volume, and mix (Solution A). Transfer 165.4 g of anhydrous sodium acetate to a 10-L volumetric flask, dilute with water to volume, and mix (Solution B). Mix 4410 mL of Solution A with 1590 mL of Solution B. Adjust, if necessary, with the addition of Solution A or Solution B to a pH of 4.2 ± 0.05.

Apparatus 2: 100 rpm.

Times: 1, 4, 10, and 15 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration ofUSP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 10%
4	between 15% and 35%
10	between 65% and 85%
15	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 8.*•2

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 4, 10, and 15 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 60% and 90%
15	not less than 80%

TEST 9—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 9.*•2

NOTE—Perform the test separately in each of the two media.

Medium 1: 0.1 N hydrochloric acid; 900 mL.

Medium 2: simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of 7.5 ± 0.1; 900 mL.

Apparatus 2: 75 rpm.

Time for Medium 1: 2 hours.

Times for Medium 2: 2, 12, 18, and 24 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with the appropriate *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved (*Medium 1*)	Amount dissolved (*Medium 2*)
2	between 0% and 5%	between 20% and 45%
12		between 35% and 55%
18		not less than 60%
24		not less than 80%

TEST 11—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 11.*•2

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 3.*

Times: 1, 6, 12, and 18 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 10%
6	between 30% and 40%
12	between 36% and 58%
18	not less than 85%

TEST 12—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 12.*•2 Proceed as directed for •*Extended-Release Dosage Forms.*•2

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 8, 14, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	not less than 65%
24	not less than 80%

TEST 13—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 13.*•2 Proceed as directed for •*Extended-Release Dosage Forms.*•2

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 8, 14, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	between 60% and 80%
24	not less than 80%

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■TEST 14—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 14.* Proceed as directed for *Extended-Release Dosage Forms.*•2

Medium, Apparatus, Times, and *Procedure*—Proceed as directed under *Test 3*.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 80%

■1S (*USP28*)

•(Official April 1, 2006)•2

Dirithromycin Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 10-mesh basket; 100 rpm.

Xanthydrol TS—[NOTE Prepare this solution daily.] To about 150 mg of xanthydrol in a 100-mL volumetric flask, add 10 mL of glacial acetic acid, and swirl to dissolve. Dilute with hydrochloric acid to volume, and mix.

Standard solution—Quantitatively dissolve an accurately weighed quantity of USP Dirithromycin RS in 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.28 mg per mL.

Procedure—After 2 hours of operation, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessel, and subject each Tablet to the test in the *Buffer stage*. Separately add 0.50 mL of acetic anhydride to 0.50 mL of the filtered solution under test and to 0.50 mL of the *Standard solution*, and mix. Add 5.0 mL of glacial acetic acid, allow to stand for 5 minutes, then add 0.50 mL of *Xanthydrol TS*, and allow 30 minutes for color development. Determine the amount of $C_{42}H_{78}N_2O_{14}$, including the 16*R*- and 16*S*-epimers, dissolved by employing UV absorption at the wavelength of maximum absorbance at about 540 nm.

BUFFER STAGE—

Medium: pH 6.8 phosphate buffer; 900 mL.

Procedure—Proceed as directed for *Acid stage* beginning with "Separately add 0.50 mL of acetic anhydride".

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{42}H_{78}N_2O_{14}$, including the 16*R*- and 16*S*-epimers, is dissolved in 45 minutes.

•(Official April 1, 2006)•2

Disopyramide Phosphate Extended-Release Capsules

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets USP •*Dissolution Test 1.*•2

pH 2.5, 0.1 M Phosphate buffer—Dissolve 272 g of monobasic potassium phosphate in 20 L of water, and adjust with hydrochloric acid to a pH of 2.50 ± 0.04. [NOTE—Do not adjust back to pH 2.50 with base if too much acid is added. It is imperative that the ionic strength of the buffer be controlled.]

Medium: pH 2.5, 0.1 M Phosphate buffer; 1000 mL.

Apparatus 1: 100 rpm.

Times: 1 hour; 2 hours; 5 hours; 12 hours.

Procedure—Filter 10 mL of the solution under test at the required test points. Determine the amount of disopyramide ($C_{21}H_{29}N_3O$) dissolved from UV absorbances at the wavelength of maximum absorbance at about 261 nm of this solution, suitably diluted with *Medium*, if necessary, using *Medium* as the blank, in comparison with a Standard solution having a known concentration of USP Disopyramide Phosphate RS dissolved in *Medium*.

Tolerances—The percentage of the labeled amount of disopyramide ($C_{21}H_{29}N_3O$) dissolved is within the range stated at each of the following times.

Time (hours)	Amount dissolved
1	between 5% and 25%
2	between 17% and 43%
5	between 50% and 80%
12	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP •*Dissolution Test 2.*•2

pH 2.5, 0.1 M Phosphate buffer, and *Procedure*—Proceed as directed for *Test 1*.

Medium—Prepare as directed for *Test 1;* 900 mL.

Apparatus 2: 100 rpm.

Times and *Tolerances:*

Time (hours)	Amount dissolved
1	between 5% and 30%
4	between 40% and 65%
8	between 60% and 90%
12	not less than 75%

•(Official April 1, 2006)•2

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Divalproex Sodium Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

■ACID STAGE—

Medium: 0.08 N hydrochloric acid (prepared by adding 40 mL of hydrochloric acid to 5000 mL of water, adjusting with 2 N hydrochloric acid to a pH of 1.2, and diluting with water to 6000 mL); 900 mL.

Apparatus 2: 50 rpm.

Time: 1 hour.

Procedure—At the end of 1 hour, carefully transfer the Tablet to a dissolution vessel containing the *Medium* of the *Buffer stage*. [NOTE—Do not perform an analysis of the *Medium* in the *Acid stage*.]

BUFFER STAGE—

Medium: pH 7.5 phosphate buffer (prepared by dissolving 40.83 g of monobasic potassium phosphate and 9.84 g of sodium hydroxide in 5000 mL of water, adjusting with 0.08 N hydrochloric acid to a pH of 7.5, and diluting with water to 6000 mL); 900 mL.

Apparatus 2: 50 rpm.

Time: 1 hour.■1S *(USP28)*

Determine the amount of $C_8H_{16}O_2$ dissolved ■in the *Buffer stage*■1S *(USP28)* by employing the following method.

Citrate buffer—Dissolve 0.5 g of citric acid monohydrate and 0.4 g of dibasic sodium phosphate in 1.0 L of water.

Potassium phosphate buffer—Dissolve 6.8 g of monobasic potassium phosphate and 1.7 g of sodium hydroxide in 1.0 L of water. Adjust with phosphoric acid to a pH of 7.4 ± 0.1.

Mobile phase—Prepare a mixture of *Citrate buffer, Potassium phosphate buffer,* and acetonitrile (35 : 35 : 30). Adjust with phosphoric acid to a pH of 3.0 ± 0.1, and mix. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Valproic Acid RS in the ■*Medium*■1S *(USP28)* used in the *Buffer stage,* having a known concentration of about 0.12 mg per mL. [NOTE—A volume of acetonitrile not exceeding 10.0% of the total volume may be used to dissolve the USP Valproic Acid RS.]

Test solution—If necessary, dilute a portion of each filtered solution under test with the ■*Medium*■1S *(USP28)* used in the *Buffer stage* to obtain a solution having a concentration of about 0.12 mg per mL.

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 4-µm packing L11. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard solution,* 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 that 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 solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of valproic acid ($C_8H_{16}O_2$) dissolved by the formula:

$$900CD(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Valproic Acid RS 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 valproic acid obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_8H_{16}O_2$ is dissolved in ■1 hour in the *Buffer stage.*■1S *(USP28)*

•(Official April 1, 2006)•2

Doxycycline Hyclate Delayed-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—[NOTE—Conduct the test by transferring the contents of each Capsule to the individual basket units of the apparatus.]

Medium: 0.06 N hydrochloric acid; 900 mL.

Apparatus 1: 50 rpm.

Time: 20 minutes.

Diluting solvent: 0.1 N hydrochloric acid.

Procedure—Determine the amount of $C_{22}H_{24}N_2O_8$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 345 nm on filtered portions of the solution under test, suitably diluted with *Diluting solvent*, in comparison with a Standard solution having a known concentration of about 0.01 mg of USP Doxycycline Hyclate RS per mL in *Diluting solvent*.

Tolerances—Level 1 (6 Capsules tested): No individual value exceeds 50% dissolved. *Level 2* (6 Capsules tested): Not more than 2 individual values of 12 tested are greater than 50% dissolved.

BUFFER STAGE—[NOTE—Conduct this stage of testing on separate specimens, selecting Capsules that were not previously subjected to *Acid-stage* testing and transferring the contents of each Capsule to the individual basket units of the apparatus.]

Medium: pH 5.5 neutralized phthalate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 1000 mL.

Apparatus 1: 50 rpm.

Time: 30 minutes.

Diluting solvent: 0.1 N hydrochloric acid.

Procedure—Determine the amount of $C_{22}H_{24}N_2O_8$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 345 nm on filtered portions of the solution under test, suitably diluted with *Diluting solvent*, in comparison with a Standard solution having a known concentration of about 0.01 mg of USP Doxycycline Hyclate RS per mL in *Diluting solvent*.

Tolerances—Not less than 85% *(Q)* of the labeled amount of $C_{22}H_{24}N_2O_8$ is dissolved in 30 minutes.

•(Official April 1, 2006)•2

Erythromycin Delayed-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

Apparatus 1: 50 rpm.

Times: 60 minutes for *Acid Stage;* 60 minutes for *Buffer Stage*.

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Procedure—Transfer the contents of 1 Capsule to the apparatus. Proceed as directed for *Acid Stage*, 900 mL of 0.06 N hydrochloric acid being placed in the vessel instead of 1000 mL of 0.1 N hydrochloric acid, and the apparatus being operated for 60 minutes instead of 2 hours. Do not perform an analysis at the end of the *Acid stage*. Continue as directed for *Buffer Stage*, 900 mL of the pH 6.8 phosphate buffer being used instead of 1000 mL. Determine the amount of $C_{37}H_{67}NO_{13}$ dissolved after 120 minutes by assaying a filtered portion of the solution under test as directed under *Antibiotics—Microbial Assays* ⟨81⟩.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{37}H_{67}NO_{13}$ is dissolved in 120 minutes.

•(Official April 1, 2006)•2

Erythromycin Delayed-Release Tablets

Change to read:

Labeling—The label indicates that the Tablets are enteric-coated. The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

Apparatus 1: 100 rpm.

Times: 60 minutes, Stage 1; 60 minutes, Stage 2.

Acid stage—Using 900 mL of simulated gastric fluid TS (prepared without pepsin) in place of 0.1 N hydrochloric acid, conduct this stage of the test for 1 hour, and do not perform an analysis of the medium.

Buffer stage—Using 900 mL of 0.05 M pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*), conduct this stage of the test for 60 minutes.

Test solution—If necessary, dilute a filtered portion of the solution under test with *Dissolution Medium* to obtain a solution having a concentration of about 0.28 mg of erythromycin per mL, and mix.

Procedure—Transfer a 2.0-mL portion of the *Test solution* to a suitable separator. Add 6 mL of pH 1.2 buffer (see *Solutions* in the section *Reagents*, *Indicators, and Solutions*), and 8 mL of a solution of bromocresol purple, prepared by dissolving 1 g of bromocresol purple in 1 L of pH 4.5 phosphate buffer, and mix. Extract with 40.0 mL of chloroform. Determine the amount of $C_{37}H_{67}NO_{13}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 410 nm using the chloroform extracts. Similarly prepare a Standard solution, having a known concentration of USP Erythromycin RS, and treat similarly.

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2 Proceed as directed under *Test 1*, except to use *Apparatus 2* at 75 rpm.

•(Official April 1, 2006)•2

Conjugated Estrogens Tablets

Change to read:

Labeling—The labeling indicates the Tablet strength and states with which in vitro •*Dissolution Test*•2 the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2 Proceed as directed for •*Extended-Release Articles.*•2

TEST 1 (for products labeled as 0.3-, ▲0.45-,▲*USP28* and 0.625-mg tablets)—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M monobasic potassium phosphate and acetonitrile (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

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

Chromatographic system—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 3.0-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.9 for equilin sulfate and 1.0 for estrone sulfate, the estrone sulfate peak being the last major peak in the chromatogram; the resolution, *R,* between equilin sulfate and estrone sulfate is not less than 1.5; and the relative standard deviation for the estrone sulfate peak is not more than 1.5%. [NOTE—If estrone is present it may be retained on the column for a period longer than 50 minutes and interfere in later chromatographic runs.]

Procedure—Separately inject equal volumes (between 20 and 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the estrone sulfate peaks. Calculate the percentage of estrone sodium sulfate released 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.

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to •*Acceptance Table 2.*•2

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

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TEST 2 (for products labeled as 0.9-mg tablets)—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2

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

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to •*Acceptance Table 2.*•2

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

TEST 3 (for products labeled as 1.25- and 2.50-mg tablets)—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3.*•2

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

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to •*Acceptance Table 2.*•2

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

•(Official April 1, 2006)•2

Felodipine Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

▲*Medium:* pH 6.5 phosphate buffer with 1% sodium lauryl sulfate; 500 mL. (*Medium* is prepared as follows. Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a 5000-mL volumetric flask. Add approximately 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5. Dilute with water to volume, and mix well.)

Apparatus 2: 50 rpm.

Times: 2, 6, and 10 hours.

Buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, *Buffer solution,* and methanol (2.5 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL.

Standard solution—Dilute an accurately measured volume of the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about 60% dissolution of a single Tablet in 500 mL of *Medium.*

Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1*). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (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 quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved in the *Medium* by the formula:

$$CD(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Felodipine RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the felodipine peak areas obtained from the *Test solution* and the *Standard solution,* respectively.▲*USP28*

Tolerances—The percentages of the labeled amount of $C_{18}H_{19}ClNO_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 42% and 68%
10	not less than 75%

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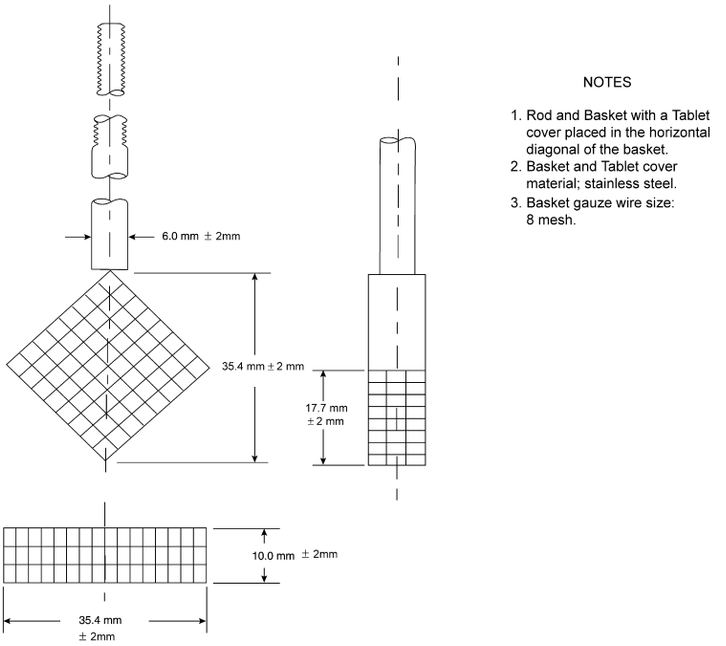

▲Fig. 1. Stationary Tablet Basket▲*USP28*

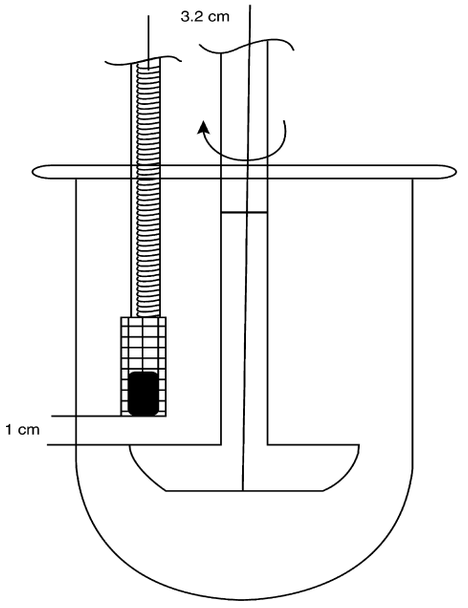

Fig. 2. Drug Release Stationary Tablet Basket Configuration Diagram

•(Official April 1, 2006)•2

Ferrous Fumarate and Docusate Sodium Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

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.

Tolerances—The percentages of the labeled amount of Fe (II) dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 40% and 75%
3	not less than 80%

•(Official April 1, 2006)•2

Garlic Delayed-Release Tablets

Change to read:

Allicin release—•Proceed as directed for *Method A* in *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms* under *Dissolution* ⟨711⟩.•2 Place a number of Tablets, equivalent to about 5 mg of potential allicin, in each vessel.

Apparatus 2: 100 rpm.

Time: 60 minutes for the *Buffer stage.*

Mobile phase, *Crude alliinase solution*, *Blank solution,* and *Chromatographic system*—Proceed as directed in the test for *Content of potential allicin.*

Standard solution—Dissolve an accurately weighed quantity of USP Alliin RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 50 µg per mL. Transfer 1.0 mL of this solution to a 5-mL volumetric flask containing 100 µL of *Crude alliinase solution*, mix, and allow to stand for 5 minutes at room temperature. Dilute with water to volume, and pass through a membrane filter having a 0.45-µm or finer porosity.

Test solution—Transfer 1.0 mL of the solution under test to a test tube containing 50 µL of 0.21 M carboxymethoxylamine hemihydrochloride. [NOTE—The solution must be transferred immediately upon removal from the dissolution vessel in order to inhibit the alliinase enzyme.]

Procedure—[NOTE—Do not perform the allicin determination in the *Acid stage.*] Determine the amount of allicin released by injecting 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 allicin peaks. Calculate the amount, in µg, of allicin released in the *Buffer stage* by the formula:

$$1050C(162.26/354.42)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Alliin RS in the *Standard solution;* 162.26 is the molecular weight of allicin; 354.42 is twice the molecular weight of alliin; and r_U and r_S are the peak responses for allicin obtained from the *Test solution* and the *Standard solution,* respectively. [NOTE—Q is the percentage of the labeled amount of potential allicin released only in the *Buffer stage.*]

•(Official April 1, 2006)•2

Hydroxyzine Hydrochloride Tablets

Change to read:

Dissolution ⟨711⟩—

▲TEST 1—

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 *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.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: water, 250 mL.

Apparatus 3: ••2 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 *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.▲*USP28*

•(Official April 1, 2006)•2

Indomethacin Extended-Release Capsules

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

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Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

Medium: pH 6.2 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 750 mL.

Apparatus 1: 75 rpm.

Times: 1, 2, 4, 6, 12, and 24 hours.

Procedure—Determine the amount of $C_{19}H_{16}ClNO_4$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 318 nm on filtered portions of the solution under test, diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Indomethacin RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 25%
2	between 20% and 40%
4	between 35% and 55%
6	between 45% and 65%
12	between 60% and 80%
24	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1*, except to use 900 mL of *Medium*.

Times: 1, 2, 4, and 12 hours.

Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 12% and 32%
2	between 27% and 52%
4	between 50% and 80%
12	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3.*•2

Medium: pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 750 mL.

Apparatus and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 2, 4, 6, 12, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{19}H_{16}ClNO_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 15% and 40%
2	between 35% and 55%
4	between 55% and 75%
6	between 65% and 85%
12	not less than 75%
24	not less than 85%

•(Official April 1, 2006)•2

Isosorbide Dinitrate Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Method B* in *Delayed-Release Dosage Forms* in *Procedure, Apparatus 1 and Apparatus 2,* except to operate the apparatus in the acid medium for 1 hour instead of 2 hours and to use *Acceptance Table 2* in *Extended-Release Dosage Forms* in *Interpretation.*•2

Apparatus 2: 50 rpm.

Times: 2, 4, and 8 hours.

Determine the amount of $C_6H_8N_2O_8$ dissolved using the following method.

Mobile phase—Prepare a filtered and degassed mixture of 0.05 M monobasic potassium phosphate and acetonitrile (52 : 48). Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, and record the chromatograms as directed for *Procedure:* the tailing factor is not more than 2.5; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of a filtered portion of the solution under test, and record the chromatograms. Determine the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium and similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_6H_8N_2O_8$ dissolved at the times specified conform to •*Acceptance Table 2.*•2 [NOTE—The test times given are cumulative, beginning with the 1 hour in the acid medium.]

Time (hours)	Amount dissolved
2	between 10% and 30%
4	between 40% and 75%
8	not less than 75%

•(Official April 1, 2006)•2

Isosorbide Dinitrate Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 2, 4, and 6 hours.

Determine the amount of $C_6H_8N_2O_8$ dissolved, using the following method.

pH 3.0 Buffer solution—Add 6.6 g of ammonium sulfate, accurately weighed, to 500 mL of water. Adjust with 1 N sulfuric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *pH 3.0 Buffer solution* (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a UV wavelength detector and a 5-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, and record the chromatograms as directed for *Procedure:* the tailing factor is not more than 2.5; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of a filtered portion of the solution under test, and record the chromatograms. Determine the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution of USP Diluted Isosorbide Dinitrate RS in the same medium, similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_6H_8N_2O_8$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 15% and 30%
2	between 50% and 70%
4	between 65% and 85%
6	not less than 75%

•(Official April 1, 2006)•2

Lansoprazole Delayed-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method A* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2

ACID STAGE—

Acid stage medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Withdraw a 25-mL aliquot and then proceed immediately as directed for *Test solution* in the *Buffer stage,* leaving the remaining 475 mL in the vessel for use in the *Buffer stage*. Using a filtered portion of the aliquot, determine the amount of $C_{16}H_{14}F_3N_3O_2S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 306 nm, using *Acid stage medium* as the blank. Concomitantly determine the absorbance of the *Acid stage* test solution in comparison with a solution of USP Lansoprazole RS, having a known concentration equivalent to about 8% of the labeled amount of lansoprazole dissolved per 500 mL of *Acid stage medium.* [NOTE—A volume of methanol not to exceed 0.5% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Acid stage medium.*]

Tolerances—Not more than 10% of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ is dissolved in 60 minutes.

BUFFER STAGE—

Buffer concentrate—Transfer 65.4 g of monobasic sodium phosphate, 28.2 g of sodium hydroxide, and 12 g of sodium dodecyl sulfate to a suitable container, and add enough water to dissolve. Dilute with water to 4 L, and mix well.

Blank solution—Prepare a mixture of *Acid stage medium* and *Buffer concentrate* (19 : 17). Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Test solution—Add 425 mL of *Buffer concentrate* to the remaining 475 mL of solution in each vessel from the *Acid stage.* Adjust, if necessary, with either phosphoric acid or sodium hydroxide to a pH of 6.8.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{16}H_{14}F_3N_3O_2S$ dissolved in filtered portions of the *Test solution*, using the difference between the absorbances at the wavelengths of about 286 nm and 650 nm, with *Blank solution* as the blank. Concomitantly determine the absorbances of the *Test solution* in comparison with the solution of USP Lansoprazole RS having a known concentration equivalent to about 70% of the labeled amount of lansoprazole dissolved in 900 mL of *Blank solution.* [NOTE—An amount of methanol not to exceed 2% of the total volume of the Standard solution may be used to dissolve USP Lansoprazole RS prior to dilution with *Blank solution.*]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{14}F_3N_3O_2S$ is dissolved in 60 minutes.

•(Official April 1, 2006)•2

Liothyronine Sodium Tablets

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing liothyronine sodium are to be made of glass.]

Medium: pH 10.0 ± 0.05 alkaline borate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 250 mL.

Apparatus 3: ••2 30 dips per minute, using 20-mesh screen on the top and 40-mesh screen on the bottom of the glass reciprocating cylinder.

Time: 45 minutes.

Determine the amount of liothyronine sodium ($C_{15}H_{12}I_3NO_4$) dissolved by employing the following method.

Ammoniated solution—Add 0.05 mL of ammonium hydroxide to 200 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55 : 45) that contains 1 mL of phosphoric acid in each 1000 mL of solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Liothyronine RS in *Ammoniated solution*, and dilute quantitatively, and stepwise if necessary, with *Ammoniated solution* to obtain a solution having a known concentration of about 10 µg of USP Liothyronine RS per mL. Dilute a portion of this solution quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 µg of USP Liothyronine RS per mL.

Test solution—Transfer 20 mL of the solution under test to a centrifuge tube, and centrifuge until a clear supernatant is obtained.

Resolution solution—Prepare a solution of USP Liothyronine RS and USP Levothyroxine RS in *Ammoniated solution* having known concentrations of about 10 µg of each USP Reference Standard per mL. Dilute with water to obtain a concentration of about 0.5 µg of each USP Reference Standard per mL.

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 L10. The flow rate is about 2 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between liothyronine and levothyroxine is not less than 3.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 200 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 $C_{15}H_{12}I_3NO_4$ dissolved.

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Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}I_3NO_4$ is dissolved in 45 minutes.

•(Official April 1, 2006)•2

Lithium Carbonate Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

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 *Medium* if necessary, and using *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 2.*•2

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 *Dissolution Test 2.*•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 2.*•2

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 *Dissolution Test 3.*•2

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 2.*•2

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 *Dissolution Test 4.*•2

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 2.*•2

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 80%

•(Official April 1, 2006)•2

Megestrol Acetate Oral Suspension

Add the following:

•**Labeling**—When more than one test for *Dissolution* is given, the labeling states the test used only if *Test 1* is not used.•2

Change to read:

Dissolution ⟨711⟩—

•TEST 1—

Medium: 0.5% sodium lauryl sulfate in water; 900 mL.

Apparatus 2: 25 rpm.

Time: 30 minutes.

Standard solution—Transfer about 45 mg, accurately weighed, of USP Megestrol Acetate RS to a 250-mL volumetric flask, add about 12 mL of methanol, and put the flask in a warm water bath until the solid is dissolved. Dilute with *Medium* to volume. The final concentration is about 18 µg of megestrol acetate per mL.

Procedure—Transfer to the surface of the *Medium* in the dissolution vessel an accurately measured volume of Oral Suspension, freshly mixed and free from air bubbles, equivalent to about 160 mg of megestrol acetate. Determine the amount of $C_{24}H_{32}O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm on filtered portions of the solution under test, in comparison with the *Standard solution.* Calculate the percentage of megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times V \times LC},$$

in which A_U and A_S are the absorbances obtained from the solution under test and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; V* is the sample volume, in mL, of Oral Suspension taken; 900 is the volume, in

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mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.5% sodium lauryl sulfate in water; 900 mL.

Apparatus 2: 25 rpm.

Time: 30 minutes.

Standard solution—Transfer about 45 mg, accurately weighed, of USP Megestrol Acetate RS to a 250-mL volumetric flask. Add about 5 mL of methanol, and mix. Dilute with *Medium* to volume. Transfer 10 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume. The final concentration is about 18 µg per mL.

Test solution—[NOTE—Use a separate syringe for each vessel.] Withdraw more than 10 mL of the Oral Suspension, using a 10-mL syringe with a long cannula. Remove air bubbles from the syringe. Adjust the volume to the 10-mL mark on the syringe, and remove the needle. Wipe the tip of the syringe, and accurately weigh (gross weight). Operate the apparatus, and rapidly dispense the Oral Suspension to the side of the vessel at about halfway from the bottom. Similarly dispense the Oral Suspension into other vessels. Accurately weigh each syringe after dispensing the sample (tare weight). Record sample weights. After completion of the dissolution, pass an aliquot through a nylon filter having a 0.45-µm porosity, and dilute 2.0 mL of the filtrate with *Medium* to 50.0 mL to obtain a solution having a theoretical concentration of about 18 µg per mL.

Procedure—Determine the amount of $C_{24}H_{32}O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm, using 0.5-cm pathlength cuvettes, on the *Test solution* in comparison with the *Standard solution*. Calculate the percentage of megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{A_U \times C_S \times 900 \times d \times 100}{A_S \times W_U \times LC},$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; d* is the density, in mg per mL, of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL; W_U is the weight, in mg, of Oral Suspension taken; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.5% sodium lauryl sulfate in degassed water; 900 mL. Use ultrapure sodium lauryl sulfate with an assay content of not less than 99.0%.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of $C_{24}H_{32}O_4$ dissolved employing the following method.

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—Transfer about 11.5 mg, accurately weighed, of USP Megestrol Acetate RS to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Proceed as directed for *Test 2,* introducing the sample into the vessel over a 10- to 15-second period (about 1 mL per second).

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.*

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 megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{r_U \times C_S \times 900 \times d \times 100}{r_S \times W_U \times LC},$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; d* is the density, in mg per mL, of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL; W_U is the weight, in mg, of Oral Suspension taken; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.●2

Mesalamine Extended-Release Capsules

Change to read:

●**Dissolution** ⟨711⟩—●2

Medium: 0.05 M pH 7.5 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate and 1 g of sodium hydroxide in water to make 1000 mL of solution, and adjusting with 10 N sodium hydroxide to a pH of 7.50 ± 0.05; ■900 mL.■1S (*USP28*)

Apparatus 2: 100 rpm.

Times: 1, 2, 4, and 8 hours.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 330 nm on filtered portions of the solution under test suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Mesalamine RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_7H_7NO_3$ dissolved at the times specified conform to ●*Acceptance Table 2.*●2

Time (hours)	Amount dissolved
1	between 5% and 25%
2	between 30% and 50%
4	between 60% and 90%
8	not less than 85%

●(Official April 1, 2006)●2

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Mesalamine Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

pH 6.0 Phosphate buffer—Transfer about 43.35 g of monobasic potassium phosphate and 1.65 g of sodium hydroxide to a 2-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.0, and mix.

Sodium hydroxide solution—Transfer 133.6 g of sodium hydroxide to a 2-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Media: 0.1 N hydrochloric acid, 500 mL for *Acid stage; pH 6.0 Phosphate buffer*, 900 mL for *Buffer stages*.

Apparatus 2: 100 rpm for *Acid stage* and for *Buffer stage 1;* 50 rpm for *Buffer stage 2*.

Times: 2 hours for *Acid stage;* 1 hour for *Buffer stage 1;* 90 minutes for *Buffer stage 2*.

ACID STAGE—After 2 hours of operation, withdraw an aliquot of the fluid, discard the remaining solution, and retain the Tablets in proper order, so that each will be returned to its respective vessel later on. Blot the Tablets with a paper towel to dry, and proceed immediately as directed for *Buffer stage 1*.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 302 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 Mesalamine RS, equivalent to about 1% of the labeled amount of $C_7H_7NO_3$, in the same *Medium*.

Tolerances—The percentage of the labeled amount of $C_7H_7NO_3$ dissolved from the units tested conforms to the *Acceptance Table* shown below. Continue testing through all levels unless the results conform at an earlier level.

BUFFER STAGE 1—[NOTE—Use buffer that has been equilibrated to a temperature of 37 ± 0.5°.] Transfer *pH 6.0 Phosphate buffer* to each of the dissolution vessels, and place each Tablet from the *Acid stage* into its respective vessel. After 1 hour remove a 50-mL aliquot, and proceed immediately as directed for *Buffer stage 2*.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 330 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 Mesalamine RS, equivalent to about 1% of the labeled amount of $C_7H_7NO_3$, in the same *Medium*.

Tolerances—The percentage of the labeled amount of $C_7H_7NO_3$ dissolved from the units tested conforms to the *Acceptance Table* shown below. Continue testing through all levels unless the results conform at an earlier level.

Acceptance Table

Level	Number Tested	Criteria
L_1	6	No individual value exceeds 1% dissolved.
L_2	6	Average of the 12 units ($L_1 + L_2$) is not more than 1% dissolved, and no individual unit is greater than 10% dissolved.
L_3	12	Average of the 24 units ($L_1 + L_2 + L_3$) is not more than 1% dissolved, and not more than one individual unit is greater than 10% dissolved.

BUFFER STAGE 2—Add 50 mL of *Sodium hydroxide solution* to each dissolution vessel to adjust to a pH of 7.2, and continue the run.

Procedure—Determine the amount of $C_7H_7NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 332 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 Mesalamine RS in the same *Medium*.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_7H_7NO_3$ is dissolved. The requirements are met if the quantities dissolved from the product conform to •*Acceptance Table 4.*•2 Continue testing through all levels unless the results conform at an earlier level.

•(Official April 1, 2006)•2

Methylphenidate Hydrochloride Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Times: 1 hour; 2 hours; 3.5 hours; 5 hours; 7 hours.

■*Test solution*—Use portions of the solution under test passed through a 0.45-µm polypropylene filter. [NOTE—Do not use glass fiber filters.]■1S *(USP28)*

Procedure—Determine the amount of $C_{14}H_{19}NO_2 \cdot HCl$ dissolved, employing the procedure set forth in the *Assay*, making any necessary volumetric adjustments.

Tolerances—The percentages of the labeled amount of $C_{14}H_{19}NO_2 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 25% and 45%
2	between 40% and 65%
3.5	between 55% and 80%
5	between 70% and 90%
7	not less than 80%

•(Official April 1, 2006)•2

Metoprolol Succinate Extended-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: pH 6.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents*, *Indicators*, *and Solutions*); 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, 8, and 20 hours.

Determine the amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved by employing the following method.

pH 3.0 Phosphate buffer, Mobile phase, and *Standard solution*—Proceed as directed in the test for *Uniformity of dosage units.*

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Procedure—Proceed as directed in the test for *Uniformity of dosage units,* except to use 5.0 mL of a filtered portion of the solution under test as the *Test solution,* and *Medium* as the blank, in comparison with a Standard solution having a known concentration of USP Metoprolol Succinate RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 25%
4	between 20% and 40%
8	between 40% and 60%
20	not less than 80%

•(Official April 1, 2006)•2

Morphine Sulfate Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•2

pH 7.5 Phosphate buffer—Dissolve 6.8 g of monobasic potassium phosphate and 1.6 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid or 2 N sodium hydroxide to a pH of 7.5.

Medium—Proceed as directed for •*Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,*•2 observing the following exceptions. Perform *Acid stage* testing, using 500 mL of 0.1 N hydrochloric acid for 1 hour; and perform *Buffer stage* testing, using 500 mL of *pH 7.5 Phosphate buffer* for not less than 8 hours.

Apparatus 1: 100 rpm.

Times: 1, 4, 6, and 9 hours.

Determine the amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and glacial acetic acid (72 : 28 : 1), containing 0.73 g of sodium 1-heptanesulfonate. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of phenol and USP Morphine Sulfate RS in *Mobile phase* to obtain a solution containing about 0.1 mg of each per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Morphine Sulfate RS in *pH 7.5 Phosphate buffer,* and dilute quantitatively, and stepwise if necessary, with *pH 7.5 Phosphate buffer* to obtain a solution having a known concentration corresponding to that of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 284-nm detector and a 3.9-mm × 30.0-cm column that contains 10-µm packing L1. The flow rate is about 2 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 phenol and 1.0 for morphine sulfate; the resolution, *R,* between the phenol and morphine sulfate peaks is not less than 2.0; the tailing factor for the morphine sulfate peak 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 25 µL) of the *Standard solution* and the filtered portion of the solution under test into the chromatograph, record the chromatograms, and measure the peak responses. Determine the amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved from the measured peak responses.

Tolerances—The percentage of the labeled amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved in 1 hour conforms to •*Acceptance Table 3.*•2 The percentages of the labeled amount of $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ dissolved at the other times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 10%
4	between 25% and 50%
6	between 50% and 90%
9	not less than 85%

•(Official April 1, 2006)•2

Nicotine Transdermal System

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: Phosphoric acid solution (1 in 1000); 250 mL, in a tall-form beaker.

Apparatus 7—Proceed as directed in the chapter, using the transdermal system holder—cylinder •(see *Figure 4b*).•2 Center the Transdermal System onto a dry, unused 10-cm × 10-cm piece of Cuprophan dialysis membrane with the adhesive side against the membrane, taking care to eliminate air bubbles between the membrane and the release surface. Attach the membrane to the cylinder using two Parker O-rings, such that one of the borders of the transdermal system is aligned to the groove and it is wrapped around the cylinder. The filled beakers are weighed and pre-equilibrated to 32.0 ± 0.3°, prior to immersing the test sample. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of 2.0 ± 0.1 cm. 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°. At the end of each release interval, allow the beakers to cool to room temperature, make up for evaporative losses by adding water to obtain the original weight, and mix. This solution is the final *Test solution*.

Times: 2, 12, and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Transfer 0.2 mL of *N,N*-dimethyloctylamine to a 1-L volumetric flask, add 220 mL of acetonitrile, and mix. Add 300 mL of water, 0.2 mL of glacial acetic acid, 0.20 g of anhydrous sodium acetate, and 0.55 g of sodium 1-dodecanesulfonate, and dilute with water to volume. Mix for 1 hour until clear. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Equilibration of the column may take as long as 3 hours.]

Standard solution—Dissolve an accurately weighed quantity of USP Nicotine Bitartrate Dihydrate RS in *Dissolution Medium*, and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a solution having a known concentration of about 0.142 mg of nicotine bitartrate per mL (or 0.046 mg nicotine as free base per mL). [NOTE—About 80 mL of this solution is required in order to prepare the *System suitability solution.*]

System suitability solution—Transfer 8 mg (free base) of nicotine to a 100-mL volumetric flask, and dissolve in 10 mL of acetonitrile. Add 5 mL of 30 percent hydrogen peroxide, and allow 15 minutes to react. Dilute with *Dissolution Medium* to volume, and mix. Transfer 20 mL of this solution to a 100-mL volumetric flask, dilute with *Standard solution* to volume, and mix.

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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 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 nicotine and any degradation peaks is not less than 1.1; 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 50 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.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified below, conforms to •*Acceptance Table 1*.•$_2$

Time (hours)	Amount dissolved
0–2	between 31% and 87%
2–12	between 62% and 191%
12–24	between 85% and 261%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2*.

Phosphate buffer—Dissolve 40.0 g of sodium chloride, 1.0 g of potassium chloride, 8.66 g of dibasic sodium phosphate, and 1.0 g of monobasic potassium phosphate in 5 L of water.

Medium: Phosphate buffer; 500 mL.

Apparatus 6: 50 rpm, double-sided tape being used to attach the Transdermal System to the cylinder.

Times: 6 and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Proceed as directed in the *Assay*.

System suitability solution—Transfer 1.0 mL of the *System suitability solution*, prepared as directed in the *Assay*, to a 100-mL volumetric flask, dilute with *Dissolution Medium* to volume, and mix.

Standard solution—Pipet 6.0 mL of the *Standard preparation*, prepared as directed in the *Assay*, into a 50-mL volumetric flask, dilute with *Dissolution Medium* to volume, and mix. Dilute quantitatively and stepwise with *Dissolution Medium* to obtain an appropriate final concentration.

Test solution—At each of the test times, withdraw a 2-mL aliquot of the solution under test. [NOTE—Replace the aliquots withdrawn for analysis with fresh portions of *Medium*.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 12.5-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution* used for the 6-hour interval, and record the peak responses as directed for *Procedure:* the resolution, *R,* between 4,4′-dipyridyl dihydrochloride and nicotine is not less than 5.0; 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 filtered portion of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to •*Acceptance Table 1*.•$_2$

Time (hours)	Amount dissolved
6	between 71% and 157%
24	between 156% and 224%

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 5: 50 rpm, the stainless steel disk assembly being replaced with a 5-cm watch glass for an 11-mg Transdermal System and an 8-cm watch glass for a 22-mg Transdermal System.

Times: 1, 2, and 4 hours.

Standard solution—Prepare a solution of USP Nicotine Bitartrate RS in water having a known concentration of nicotine similar to that of the solution under test.

Procedure—Determine the amount of $C_{10}H_{14}N_2$ released by employing UV absorption at the wavelength of maximum absorbance at about 259 nm, in comparison with the *Standard solution*, using water as the blank.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to the following *Acceptance Table*.

Time (hours)	Amount dissolved
1	between 35% and 75%
2	between 55% and 95%
4	not less than 73%

Acceptance Table

Level	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 5% of the labeled content outside each of the stated ranges; and none is more than 5% of the 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 5% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 5% of the labeled content below the stated amount at the final test time; and none of the units is more than 10% of the labeled content outside each of the stated ranges or more than 10% of the labeled content below the stated amount at the final test time.

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

Medium: 0.025 N hydrochloric acid; 600 mL.

Apparatus 5: 50 rpm, a convex screen being used to hold the Transdermal System in position during testing.

Times: 4 and 16 hours.

Standard solution and *Procedure*—Proceed as directed under *Test 3*.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to •*Acceptance Table 1*.•$_2$

Time (hours)	Amount dissolved
4	between 36% and 66%
16	between 72% and 112%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.

Phosphate buffer, Medium, and *Apparatus*—Proceed as directed under *Test 2*.

Times: 3, 6, and 24 hours.

Mobile phase—Proceed as directed in the *Assay*.

System suitability solution, *Standard solution*, *Test solution*, and *Chromatographic system*—Proceed as directed under *Test 2*.

Procedure—Proceed as directed under *Test 2* except to inject about 30 µL.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to •*Acceptance Table 1*.•$_2$

Time (hours)	Amount dissolved
3	between 79% and 112%
6	between 108% and 141%
24	between 156% and 202%

•(Official April 1, 2006)•$_2$

Nifedipine Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•$_2$ with which the product complies.

•(Official April 1, 2006)•$_2$

Change to read:

•**Dissolution** ⟨711⟩—•$_2$

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1*.•$_2$

Medium: water; 50 mL.

Apparatus 7 •(see *Drug Release* ⟨724⟩):•$_2$ ■15 to 30 cycles per minute.■1S (*USP28*) 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°. ■At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.■1S (*USP28*)

Times: 4, ■8, 12, 16, 20, and 24 hours.

Diluting solution: a mixture of methanol and water (1 : 1).■1S (*USP28*)

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of ■methanol,■1S (*USP28*) dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with ■*Diluting solution* to obtain solutions having suitable known concentrations.

Test solution—Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise, if necessary, with *Diluting solution* to obtain a final mixture consisting of equal parts of methanol and water.■1S (*USP28*)

Procedure—■Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Test solution* at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. [NOTE—For the 4-hour time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]■1S (*USP28*)

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 2*.•$_2$ ■

Time (hours)	Amount dissolved*
4	between 5% and 17%
8	—
12	between 43% and 80%
16	—
20	—
24	not less than 80%

* The amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.■1S (*USP28*)

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2*.•$_2$

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L 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 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm, with sinkers (see *Figure 1*).

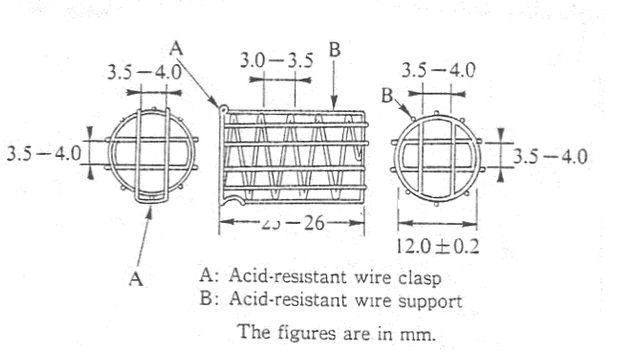

Fig. 1 (printed with permission of the Japanese Pharmacopoeia)

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 *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%.

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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 2*.•2

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 *Dissolution Test 3*.•2

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; ■900 mL.■1S (*USP28*)

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. [NOTE—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 *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 *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 0.034 mg of USP Nifedipine RS per mL. [NOTE—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 *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 2*.•2

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; ■900 mL.■1S (*USP28*)

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 *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 *Medium* as the blank.

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.

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. [NOTE—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 *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 2*.•2

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 *Dissolution Test 4*.•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, 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. [NOTE—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 the *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 2*.•2

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%

•(Official April 1, 2006)•2

Nitrofurantoin Capsules

Change to read:

Dissolution ⟨711⟩—

TEST 1 (where it is 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 *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 point conforms to •*Acceptance Table 2,*•2 and the percentages dissolved at the 3- and 8-hour points conform to the criteria for the final test time in •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 20% and 60%
3	not less than 45%
8	not less than 60%

TEST 2 (where it is 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 for 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 L, 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*).

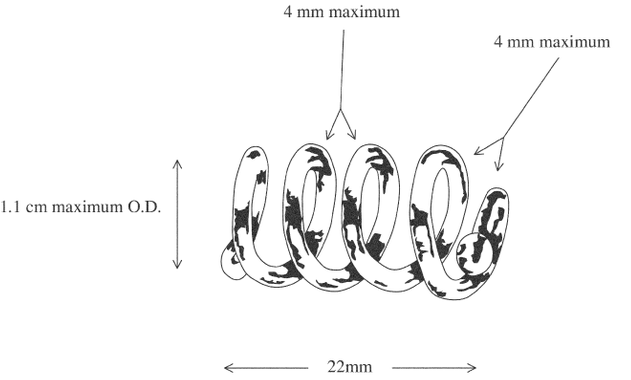

Fig. 1. Sinker.

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, suitably 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 of $C_8H_6N_4O_5$ dissolved at the specified times conform to the accompanying *Acceptance Table.*

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%

Acceptance Table

Level	Number Tested	Criteria
L_1	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.
L_2	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. 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 are less than the stated amount at the final test time.

•(Official April 1, 2006)•2

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Omeprazole Delayed-Release Capsules

Change to read:

Labeling—When more than one •*Dissolution Test*•$_2$ is given, the labeling states the •*Dissolution Test*•$_2$ used only if *Test 1* is not used.

•(Official April 1, 2006)•$_2$

Change to read:

•**Dissolution** ⟨711⟩—•$_2$

TEST 1—••$_2$

ACID RESISTANCE STAGE—

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 100 rpm.

Time: 2 hours.

pH 7.6 Phosphate buffer, Mobile phase, and *Chromatographic system*—Proceed as directed for *Buffer stage.*

Standard solution—Transfer about 50 mg of USP Omeprazole RS, accurately weighed, to a 250-mL volumetric flask, dissolve in 50 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix. Transfer 10.0 mL of this solution into a 100-mL volumetric flask, add 20 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix.

Test solution—After 2 hours, filter the *Dissolution Medium* containing the pellets through a sieve with an aperture of not more than 0.2 mm. Collect the pellets on the sieve, and rinse them with water. Using approximately 60 mL of 0.01 M sodium borate solution, carefully transfer the pellets quantitatively to a 100-mL volumetric flask. Sonicate for about 20 minutes until the pellets are broken up. Add 20 mL of alcohol to the flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropriate amount of this solution with 0.01 M sodium borate solution to obtain a solution having a concentration of about 0.02 mg per mL. •At level L_1, test 6 units. Test 6 additional units at level L_2, and at level L_3, an additional 12 units are tested. Continue testing through the three levels unless the results conform at either L_1 or L_2.•$_2$

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in the *Medium* by the formula:

$$T - CD(r_U / r_S),$$

in which T is the labeled quantity, in mg, of omeprazole in the capsule; C is the concentration, in mg per mL, of USP Omeprazole RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Level L_1*:* no individual value exceeds 15% of omeprazole dissolved. Level L_2*:* the average of 12 units is not more than 20% of omeprazole dissolved, and no individual unit is greater than 35% of omeprazole dissolved. Level L_3*:* the average of 24 units is not more than 20% of omeprazole dissolved, not more than 2 units are greater than 35% of omeprazole dissolved, and no individual unit is greater than 45% of omeprazole dissolved.

BUFFER STAGE—

Medium: pH 6.8 phosphate buffer, 900 mL.

Proceed as directed for *Acid resistance stage* with a new set of capsules from the same batch. After 2 hours, add 400 mL of 0.235 M dibasic sodium phosphate to the 500 mL of 0.1 N hydrochloric acid medium in the vessel. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Apparatus 2: 100 rpm.

At the end of 30 minutes, determine the amount of $C_{17}H_{19}N_3O_3S$ dissolved in pH 6.8 phosphate buffer by employing the following method.

pH 10.4, 0.235 M Dibasic sodium phosphate—Dissolve 33.36 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with 2 N sodium hydroxide to a pH of 10.4 ± 0.1.

pH 6.8 Phosphate buffer—Add 400 mL of 0.1 N hydrochloric acid to 320 mL of *pH 10.4, 0.235 M Dibasic sodium phosphate,* and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 6.8 ± 0.05.

pH 7.6 Phosphate buffer—Dissolve 0.718 g of monobasic sodium phosphate and 4.49 g of dibasic sodium phosphate in 1000 mL of water. Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of 7.6 ± 0.1. Dilute 250 mL of this solution with water to 1000 mL.

Mobile phase—Transfer 340 mL of acetonitrile to a 1000-mL volumetric flask, dilute with *pH 7.6 Phosphate buffer* to volume, and pass through a membrane filter having a 0.5-µm or finer porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution 1 (for Capsules labeled 10 mg)—Dissolve an accurately weighed quantity of USP Omeprazole RS in alcohol to obtain a solution having a known concentration of about 2 mg per mL. Dilute with *pH 6.8 Phosphate buffer* quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.01 mg per mL. Immediately add 2 mL of 0.25 M sodium hydroxide to 10 mL of this solution, and mix. [NOTE—Do not allow the solution to stand before adding the sodium hydroxide solution.]

Standard solution 2 (for Capsules labeled 20 mg and 40 mg)—Proceed as directed for *Standard solution 1,* except to obtain a solution having a known concentration of about 0.02 mg per mL before mixing with 2 mL of 0.25 M sodium hydroxide.

Test solution 1 (for Capsules containing 10 mg and 20 mg)—Immediately transfer 5.0 mL of the solution under test to a test tube containing 1.0 mL of 0.25 M sodium hydroxide. Mix well, and pass through a membrane filter having a 1.2-µm or finer porosity. Protect from light.

Test solution 2 (for Capsules labeled 40 mg)—Immediately transfer 5.0 mL of the solution under test to a test tube containing 2.0 mL of 0.25 M sodium hydroxide and 5 mL of *pH 6.8 Phosphate buffer.* Mix well, and pass through a membrane filter having a 1.2-µm or finer porosity. Protect from light.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 12.5-cm analytical column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the appropriate *Standard solution,* and record the peak responses as directed for *Procedure:* 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 20 µL) of the appropriate *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved by the formula:

$$VCD(r_U / r_S),$$

in which V is the volume of *Medium* in each vessel; C is the concentration, in mg per mL, of USP Omeprazole RS in the appropriate *Standard solution; D* is the dilution factor used in preparing the appropriate *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from the appropriate *Test solution* and the *Standard solution,* respectively.

Tolerances—For Capsules labeled 10 and 20 mg, not less than 75% *(Q)* of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 30 minutes. For Capsules labeled 40 mg, not less than 70% (*Q*) of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 30 minutes. •The requirements are met if the quantities dissolved from the product conform to *Acceptance Table 1.*•$_2$

TEST 2 —•$_{\bullet 2}$ If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*$_{\bullet 2}$

ACID RESISTANCE STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 2 hours.

Procedure—After 2 hours, remove each sample from the basket, and quantitatively transfer into separate volumetric flasks to obtain a solution having a final concentration of about 0.2 mg per mL. Proceed as directed for the *Assay preparation* in the *Assay,* starting with "Add about 50 mL of *Diluent*". Calculate the quantity, in mg, of omeprazole ($C_{17}H_{19}N_3O_3S$) dissolved in the *Medium* by the formula:

$$T - CD(r_U / r_S),$$

in which T is the assayed quantity, in mg, of omeprazole in the capsule; C is the concentration, in mg per mL, of USP Omeprazole RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the omeprazole peak responses obtained from *Test solution* and *Standard solution,* respectively.

Tolerances—It complies with the following *Acceptance Table:*

Acceptance Table

Level	Criterion
L_1	the average of the 6 units is not more than 10% of omeprazole dissolved
L_2	the average of the 12 units is not more than 10% of omeprazole dissolved
L_3	the average of the 24 units is not more than 10% of omeprazole dissolved

BUFFER STAGE—

Medium: 0.05 M pH 6.8 phosphate buffer; 900 mL (see *Reagents, Indicators, and Solutions*).

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Proceed as directed for *Acid resistance stage* with a new set of capsules from the same batch. After 2 hours, replace the acid medium with the buffer medium and continue the test for 45 more minutes. Determine the amount of $C_{17}H_{19}N_3O_3S$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 305 nm on portions of the solutions under test passed through a 0.2-µm nylon filter, in comparison with a Standard solution having a known concentration of USP Omeprazole RS in the same *Medium.*

Tolerances—It complies with •*Acceptance Table 1*$_{\bullet 2}$ under *Dissolution* ⟨711⟩. Not less than 75% *(Q)* of the labeled amount of $C_{17}H_{19}N_3O_3S$ is dissolved in 45 minutes.

•(Official April 1, 2006)$_{\bullet 2}$

Oxandrolone Tablets

Delete the following:

•**Disintegration** ⟨701⟩: 15 minutes.$_{\bullet 2}$

Add the following:

•**Dissolution** ⟨711⟩—

Medium: a solution of water and isopropanol (7 : 3); 500 mL.

Apparatus 2: 100 rpm.

Time: 60 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Internal standard solution—Dissolve accurately weighed quantities of 17α-methyl testosterone, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.2 mg per mL (for tablets with 2.5-mg label claim) and about 0.8 mg per mL (for tablets with 10-mg label claim).

Standard solution—Dissolve an accurately weighed quantity of USP Oxandrolone RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 1 mg per mL.

Working standard solution—Combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polytef filter. Transfer 20 mL of the filtrate to a separatory funnel, add 400 µL of the *Internal standard solution,* 40 mL of 10% potassium chloride solution, and 8 mL of chloroform. In separate separatory funnels, prepare an extraction blank and an internal standard blank in a similar manner using 20 mL of filtered *Medium* in place of the solution under test and excluding the *Internal standard solution* from the extraction blank. Shake each funnel, and allow the layers to separate. Collect the lower chloroform layer. Repeat the extraction procedure one more time. Evaporate the solvents under a stream of nitrogen at 45° until just dry. Reconstitute the dried residue with 2 mL of acetonitrile (for tablets with 2.5-mg label claim) or with 8 mL of acetonitrile (for tablets with 10-mg label claim), and sonicate for 10 minutes.

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 0.5-µm phase G27. The carrier gas is helium, flowing at a rate of about 16.8 mL per minute. The injection port and detector temperatures are maintained at 190° and 320°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is increased at a rate of 25° per minute to 280°, and maintained at 280° for 3 minutes. Then the column temperature is increased at a rate of 10° per minute to 320°, and maintained at 320° for 3 minutes. Chromatograph the acetonitrile, the extraction blank, and the internal standard blank, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5. Make two injections of the *Working standard solution,* and record the peak responses. The average oxandrolone/*Internal standard solution* peak area percent comparison is between 98.0% and 102.0%. The resolution, *R,* between the oxandrolone peak and the nearest eluting peak is equal to or greater than 1.5.

Procedure—Separately inject equal volumes (0.5 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 $C_{19}H_{30}O_3$ released by the formula:

$$\frac{C_S \times \text{sample ratio} \times V_{UF} \times 500 \times 100}{\text{Standard ratio} \times V_{UI} \times LC},$$

in which C_S is the concentration, in mg per mL, of oxandrolone in the *Standard solution;* sample ratio is the area ratio of oxandrolone to 17α-methyltestosterone in the sample injection for each *Test solution;* V_{UF} is the final volume, in mL, of the sample after reconstitution of the dry residue; 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; standard ratio is the mean area ratio of oxandrolone to 17α-methyltestosterone in all injec-

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tions of the *Standard solution;* V_{UI} is the initial sample volume, in mL, used in the extraction; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of oxandrolone ($C_{19}H_{30}O_3$) is dissolved in 60 minutes.●2

Oxprenolol Hydrochloride Extended-Release Tablets

Change to read:

●**Dissolution** ⟨711⟩—●2

Acid medium: 0.1 N hydrochloric acid; 900 mL.

Dissolution medium: simulated intestinal fluid TS (without enzyme); 900 mL.

Apparatus 1: 100 rpm.

Times: 1 hour in *Acid medium;* 1, 3, and 7 hours in *Dissolution medium*.

Procedure—Determine the amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorption at about 272 nm on the first solution under test, suitably diluted with *Acid medium,* in comparison with a Standard solution having a known concentration of USP Oxprenolol Hydrochloride RS in the same medium. Promptly transfer the basket containing the Tablet to *Dissolution medium*. After 1, 3, and 7 hours, respectively, remove 9.0 mL of the test solution and determine the amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorption at about 272 nm on the solution under test, suitably diluted with *Dissolution medium,* in comparison with a Standard solution having a known concentration of USP Oxprenolol Hydrochloride RS in the same medium. [NOTE—Replace the aliquots withdrawn for analysis with fresh portions of *Dissolution medium*.]

Tolerances—The percentages of the labeled amount of $C_{15}H_{23}NO_3 \cdot HCl$ dissolved at the times specified conform to ●*Acceptance Table 2.*●2

Time (hours)	Amount dissolved
1, in *Acid medium*	between 15% and 45%
1, in *Dissolution medium*	between 30% and 60%
3, in *Dissolution medium*	between 50% and 80%
7, in *Dissolution medium*	not less than 75%

●(Official April 1, 2006)●2

Oxtriphylline Extended-Release Tablets

Change to read:

Labeling—Label the Tablets to state both the content of oxtriphylline and the content of anhydrous theophylline. ●The labeling indicates the *Dissolution Test* with which the product complies.●2

●(Official April 1, 2006)●2

Change to read:

●**Dissolution** ⟨711⟩—●2

TEST 1 (for products labeled as 400-mg tablets)—If the product complies with this test, the labeling indicates that it meets ●USP *Dissolution Test 1.* Proceed as directed for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*●2

pH 7.5 Buffer—Transfer 27.22 g of monobasic potassium phosphate to a 4-L volumetric flask, add 1 L of water and 816 mL of 0.2 N sodium hydroxide, and dilute with water to about 3800 mL. Adjust with 0.2 N sodium hydroxide or phosphoric acid to a pH of 7.5, and dilute with water to volume.

Medium: 0.1 N hydrochloric acid for the first hour, then *pH 7.5 Buffer*; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Determine the amount of $C_{12}H_{21}N_5O_3$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 248 nm on filtered portions of the solution under test, diluted with *Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Oxtriphylline RS in the same *Medium*.

Times and *Tolerances*—

Time (hours)	Amount dissolved
1	between 5% and 30%
3	between 50% and 70%
5	between 65% and 85%
7	not less than 75%

TEST 2 (for products labeled as 600-mg tablets)—If the product complies with this test, the labeling indicates that it meets ●USP *Dissolution Test 2.* Proceed as directed for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*●2

pH 7.5 Buffer, Apparatus, Medium, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances*—

Time (hours)	Amount dissolved
1	between 15% and 40%
3	between 50% and 70%
7	not less than 75%

●(Official April 1, 2006)●2

Pentoxifylline Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the ●*Dissolution Test*●2 with which the product complies.

●(Official April 1, 2006)●2

Change to read:

●**Dissolution** ⟨711⟩—●2

TEST 1—If the product complies with this test, the labeling indicates that it meets ●USP *Dissolution Test 1.*●2

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 *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 2.*•2

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 *Dissolution Test 2.*•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 78%
20	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3.*•2

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 *Dissolution Test 4.*•2

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 *Dissolution Test 5.*•2

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 *Dissolution Test 6.*•2

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 *Dissolution Test 7.*•2

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 *Dissolution Test 8.*•2

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%

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TEST 9—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 9.*•2

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 *Dissolution Test 10.*•2

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%

•(Official April 1, 2006)•2

Phenylpropanolamine Hydrochloride Extended-Release Capsules

Change to read:

Labeling—The labeling indicates the •USP *Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

Medium: water; 1000 mL.

Apparatus 1: 100 rpm.

Times: 3, 6, and 12 hours.

Determine the amount of $C_9H_{13}NO \cdot HCl$ dissolved by employing the following method.

Solvent A—Dissolve 1.9 g of sodium 1-hexanesulfonate in 700 mL of water, add 50 mL of 1 M monobasic sodium phosphate and 20 mL of 0.25 N triethylammonium phosphate (prepared by mixing 500 mL of a solution containing 25.3 g of triethylamine and 500 mL of a solution containing 9.6 g of phosphoric acid), and mix. Dilute with water to 1 L, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solvent A* and methanol (100 : 82). Make adjustments if necessary (see *System Suitablity* under *Chromatography* ⟨621⟩).

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 L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of a Standard solution, and record the peak 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 2%.

Procedure—Inject an accurately measured volume (about 50 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 $C_9H_{13}NO \cdot HCl$ dissolved by comparison with a Standard solution having a known concentration of USP Phenylpropanolamine Hydrochloride RS in the same *Medium* and similarly chromatographed.

Tolerances—The percentages of the labeled amount of $C_9H_{13}NO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2*•2

Time (hours)	Amount dissolved
3	between 15% and 45%
6	between 40% and 70%
12	not less than 70%

•(Official April 1, 2006)•2

Phenylpropanolamine Hydrochloride Extended-Release Tablets

Change to read:

Labeling—The labeling states the in vitro •*Dissolution*•2 test conditions of *Times* and *Tolerances,* as directed under •*Dissolution.*•2

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

Medium: water; 1000 mL.

Apparatus 1: 100 rpm.

Times and *Tolerances:* as specified in the *Labeling*; use •*Acceptance Table 2.*•2

Determine the amount of $C_9H_{13}NO \cdot HCl$ dissolved, employing the following method.

Solvent A, *Mobile phase*, *Chromatographic system*, and *Procedure*—Proceed as directed in *Test 1* for •*Dissolution*•2 under *Phenylpropanolamine Hydrochloride Extended-Release Capsules*.

•(Official April 1, 2006)•2

Interim Revision Announcement

Pilocarpine Ocular System

Change to read:

Drug release pattern—Place each of the Ocular Systems in suitable porous holders made of an inert material, and suspend each from a nickel wire. To the upper end of the wire attach a tag identifying the specimen. Put each assembly into a test tube containing 27.0 mL of saline TS so that the system lies at the bottom of the tube and the identifying tag extends from the open top of the tube. Put the tubes into a horizontally reciprocating shaker in which the temperature is maintained at 37 ± 0.5°. Agitate the tubes with a horizontal amplitude of about 4 cm and a frequency of about 35 cycles per minute. At 7, 24, 48, 72, 96, and 168 hours, remove the assemblies from their tubes, and each time replace them in similar tubes containing 27.0 mL of fresh saline TS. Determine the amount of pilocarpine in solution in each tube, after adjusting the volume to 27.0 mL to make up for any evaporative losses, by measuring the UV absorbance in 1-cm cells at the wavelength of maximum absorbance at about 215 nm, with a suitable spectrophotometer, against saline TS as the blank. Concomitantly measure the absorbance of a Standard solution of USP Pilocarpine Hydrochloride RS having a known concentration of about 20 µg in each mL of saline TS. Calculate the quantity, in µg, of $C_{11}H_{16}N_2O_2$ in each solution taken by the formula:

$$(208.26 / 244.72)(A_U / A_S)27C,$$

in which 208.26 and 244.72 are the molecular weights of pilocarpine and pilocarpine hydrochloride, respectively; A_U and A_S are the absorbances of the test solution and the Standard solution, respectively; and C is the concentration, in µg per mL, of USP Pilocarpine Hydrochloride RS in the Standard solution. Calculate the amount of pilocarpine released in 168 hours by adding the pilocarpine content of each set of tubes collected over 168 hours.

Tolerances—The amount of $C_{11}H_{16}N_2O_2$ from each Ocular System released during the total 0 to 168 hours tested conforms to •*Acceptance Table 1*•2 under *Drug Release* ⟨724⟩. The drug release range for this time period is not less than 80.0% and not more than 120.0% of the labeled release pattern.

•(Official April 1, 2006)•2

Procainamide Hydrochloride Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 1.*•2

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, and 6 hours.

Procedure—Determine the amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 224 nm, using filtered portions of the solution under test, diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Procainamide Hydrochloride RS in the same *Medium*.

Tolerances—The percentage of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved •at the times specified conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
6	not less than 75%

TEST 2—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 2.*•2

Medium—Proceed as directed for *Method B* under •*Delayed-Release Dosage Forms.*•2

ACID STAGE: 0.1 N hydrochloric acid; 900 mL for 1 hour.

BUFFER STAGE: 0.05 M phosphate buffer, pH 7.5; 900 mL (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*) for not less than 8 hours.

Apparatus 2: 50 rpm, with sinkers.

Times: 1, 4, and 8 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1.*

Tolerances—••2 The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 3.*•2

Medium—Proceed as directed under *Test 2.*

Apparatus 2: 50 rpm, with sinkers.

Times: 1, 3, 6, and 8 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1.*

Tolerances—••2 The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 25% and 50%
3	between 40% and 75%
6	between 65% and 90%
8	not less than 80%

TEST 4—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 4.*•2

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 50 rpm.

Times: 1, 2, 4, 8, and 14 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1.*

Tolerances—••2 The percentages of the labeled amount of $C_{13}H_{21}N_3O \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 30%
2	between 25% and 45%
4	between 45% and 75%
8	between 70% and 90%
14	not less than 80%

TEST 5—If the product complies with this test the labeling indicates that the product meets •USP *Dissolution Test 5*.•2

Medium—Proceed as directed for *Method B* under •*Delayed-Release Dosage Forms*.•2

ACID STAGE: 0.1 N hydrochloric acid; 1000 mL for 1 hour.

BUFFER STAGE: 0.05 M phosphate buffer, pH 7.5; 1000 mL (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*) for not less than 8 hours.

Apparatus 2: 50 rpm, with sinkers.

Times: 1, 4, 6, and 8 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1*.

Tolerances—Proceed as directed for *Tolerances* in *Test 2*.

FOR 500 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 45%
4	between 55% and 75%
6	not less than 65%
8	not less than 75%

FOR 750 AND 1000 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
6	between 70% and 90%
8	not less than 75%

TEST 6—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 6*.•2

Medium—Proceed as directed for *Test 2*.

Apparatus 2: 50 rpm.

Times: 1, 4, and 8 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1*.

Tolerances—Proceed as directed for *Tolerances* in *Test 2*.

FOR 250 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 60%
4	between 60% and 90%
8	not less than 80%

FOR 500 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
8	not less than 85%

FOR 750 MG TABLETS—

Time (hours)	Amount dissolved
1	between 30% and 50%
4	between 60% and 80%
8	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that the product meets •USP *Dissolution Test 8*.•2

Medium—Proceed as directed for *Method B* under •*Delayed-Release Dosage Forms*.•2

ACID STAGE: 0.1 N hydrochloric acid; 900 mL for 1 hour.

BUFFER STAGE: 0.05 M phosphate buffer, pH 7.5; 900 mL (see *Buffer Solutions* under *Reagents*, *Indicators, and Solutions*) for not less than 8 hours.

Apparatus 2: 50 rpm, with sinkers.

Times: 1, 4, 6, and 8 hours.

Procedure—Proceed as directed for *Procedure* in *Test 1*.

Tolerances—Proceed as directed for *Tolerances* in *Test 2*.

Time (hours)	Amount dissolved
1	between 33% and 50%
4	between 70% and 85%
6	not less than 80%
8	not less than 85%

•(Official April 1, 2006)•2

Progesterone Intrauterine Contraceptive System

Change to read:

Drug release pattern—Remove the attached sutures from 10 Systems, and secure each system to a corrosion-resistant wire of sufficient length such that the systems are completely immersed during the shaking operation but do not touch the bottoms of the flasks. Suspend each system by the attached wire from the arm of a mechanical shaker designed to travel 2.5 cm in each direction in a vertically reciprocating cycle, at a speed of 2.5 cycles per second, so that each system is immersed in a separate 250-mL volumetric flask containing 230 mL of water, pre-equilibrated to 60 ± 0.1°. Immerse the volumetric flasks in an insulated constant-temperature water bath, maintained at 60 ± 0.1° and having a suitable means of maintaining the water level, so that the water level of the bath is above the water level in the flasks. Employ a rack or other suitable means of support for the flasks in the water bath.

Operate the shaker under the conditions described above for 23.5 hours, then remove the flasks and the systems from the bath. Remove the systems from the flasks, and immerse each system in a different flask containing 230 mL of water, pre-equilibrated to 60 ± 0.1°, and immerse these flasks in the water bath. Repeat this shaking operation daily for 12 days, using different flasks each day.

Determine the quantity of progesterone in the solutions from each of the 12 days of testing as follows. Immediately add 15 mL of methanol to each solution, allow to cool to room temperature, dilute with water to volume, and mix. Concomitantly determine the UV absorbances of each test solution and of a solution of USP Progesterone RS in the same medium, having a known concentration of about 7 µg per mL, in 2-cm cells at the wavelength of maximum absorbance at about 248 nm, with a suitable spectrophotometer, against a blank of water and methanol (47 : 3). Calculate the progesterone release rate, in mg per day, in the solutions taken by the formula:

$$(A_U / A_S)(24 / 23.5)0.25C,$$

in which A_U and A_S are the absorbances of the test solution and the Standard solution, respectively; and C is the concentration, in µg per mL, of USP Progesterone RS in the Standard solution. For the time points specified, the drug-release pattern conforms to •*Acceptance Table 1*•2 under *Drug Release* ⟨724⟩.

Day	Release Rate (mg per day)
6	1.05–1.45
9	0.95–1.35
12	0.90–1.30

•(Official April 1, 2006)•2

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Propranolol Hydrochloride Extended-Release Capsules

Change to read:

Labeling—The labeling states the •*Dissolution Test* •2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•2

pH 1.2 Buffer solution—Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, dilute with water to 1 L, and mix.

pH 6.8 Buffer solution—Dissolve 21.72 g of anhydrous dibasic sodium phosphate and 4.94 g of citric acid monohydrate in water, dilute with water to 1 L, and mix.

Media—Proceed as directed under *Method B* for •*Delayed-Release Dosage Forms,*•2 using 900 mL of *pH 1.2 Buffer solution* during the *Acid stage,* run for 1.5 hours, and use the acceptance criteria given under *Tolerances*. For the *Buffer stage*, use 900 mL of *pH 6.8 Buffer solution*, run for the time specified, and use the acceptance criteria given under *Tolerances*.

Apparatus 1: 100 rpm.

Times: 1.5, 4, 8, 14, and 24 hours.

Procedure—Using filtered portions of the solution under test, diluted if necessary, determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, by comparison with a Standard solution in water having a known concentration of USP Propranolol Hydrochloride RS.

Tolerances—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2.

Time (hours)	Amount dissolved
1.5	not more than 30%
4	between 35% and 60%
8	between 55% and 80%
14	between 70% and 95%
24	between 81% and 110%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2

pH 1.2 Buffer solution—Dissolve 2.0 g of sodium chloride in water, add 7.0 mL of hydrochloric acid, dilute with water to 1 L, and mix.

pH 7.5 Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate and 1.6 g of sodium hydroxide in 900 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.5, dilute with water to 1 L, and mix.

Media—Proceed as directed under *Method B* for •*Delayed-Release Dosage Forms,*•2 using 900 mL of *pH 1.2 Buffer solution* during the *Acid stage,* run for 1 hour, and use the acceptance criteria given under *Tolerances*. For the *Buffer stage*, use 900 mL of *pH 7.5 Buffer solution*, run for the time specified, and use the acceptance criteria given under *Tolerances.*

Apparatus 1: 50 rpm.

Times: 1 hour, 3, 6, and 12 hours.

Procedure—Using filtered portions of the solution under test, diluted if necessary, determine the amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved, using UV absorbances at the wavelength of maximum absorbance at about 320 nm, with respect to a baseline drawn from 355 nm through 340 nm, by comparison with a Standard solution in water having a known concentration of USP Propranolol Hydrochloride RS.

Tolerances—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	not more than 20%
3	between 20% and 45%
6	between 45% and 80%
12	not less than 80%

•(Official April 1, 2006)•2

Propranolol Hydrochloride and Hydrochlorothiazide Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•2

pH 1.5 Buffer solution, pH 6.8 Buffer solution, Media, and *Apparatus*—Proceed as directed in the test for •*Dissolution*•2 under *Propranolol Hydrochloride Extended-Release Capsules*.

Analytical method—Determine the amounts of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) and propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved, using the following method.

Stock standard solution A—Prepare a solution of USP Propranolol Hydrochloride RS in dilute hydrochloric acid (1 in 100) having a known concentration of about 0.4 mg per mL.

Stock standard solution B—Dissolve an accurately weighed quantity of USP Hydrochlorothiazide RS in 0.25 N sodium hydroxide to obtain a solution having a concentration of about 25 mg per mL. Quantitatively dilute this solution with water to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard solution—Prepare, by combining aliquots of *Stock standard solutions*, *A* and *B*, and diluting with dilute hydrochloric acid (1 in 100), solutions bracketing the expected concentration of the samples at the various time points.

Times: 30 minutes; 1.5, 4, 8, 14, and 24 hours.

Procedure—Use an automatic analyzer consisting of a liquid sampler, a proportioning pump, two UV spectrophotometers, and a manifold consisting of the components illustrated in the diagram under *Automated Methods of Analysis* ⟨16⟩. Start the sampler and conduct determinations at a rate of 30 per hour, using a ratio of about 1 : 1 for the sample to wash time. Calculate the amounts of $C_7H_8ClN_3O_4S_2$ and $C_{16}H_{21}NO_2 \cdot HCl$ dissolved by comparison with the *Standard solution.*

Tolerances (*Hydrochlorothiazide*)—Use •*Acceptance Table 1.*•2 Not less than 80% *(Q)* of the labeled amount of $C_7H_8ClN_3O_4S_2$ is dissolved in 30 minutes.

Tolerances (*Propranolol Hydrochloride*)—The percentages of the labeled amount of $C_{16}H_{21}NO_2 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved (%)
1.5	not more than 30%
4	between 35% and 60%
8	between 55% and 80%
14	between 70% and 95%
24	between 83% and 108%

•(Official April 1, 2006)•$_2$

Pseudoephedrine Hydrochloride Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•$_2$

Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 3, 6, and 12 hours.

Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved, employing the procedure set forth in the *Assay,* using a filtered portion of the solution under test as the *Assay preparation* in comparison with a Standard solution having a known concentration of USP Pseudoephedrine Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_2$

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 45% and 75%
12	not less than 75%

•(Official April 1, 2006)•$_2$

Pseudoephedrine Hydrochloride Extended-Release Tablets

Change to read:

Labeling—When more than one •*Dissolution Test*•$_2$ is given, the labeling states the •*Dissolution Test*•$_2$ used only if *Test 1* is not used.

•(Official April 1, 2006)•$_2$

Change to read:

•**Dissolution** ⟨711⟩—•$_2$

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*—•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2.*•$_2$

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 *Dissolution Test 3.*•$_2$

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*—•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2.*•$_2$

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 *Dissolution Test 2.*•$_2$

Medium: 0.9% sodium chloride in water; 50 mL.

Apparatus 7 •(see *Drug Release* ⟨724⟩):•$_2$ 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.

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4. Insert rod •(see *Figure 4c* under *Drug Release* ⟨724⟩)•$_{2}$ 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.

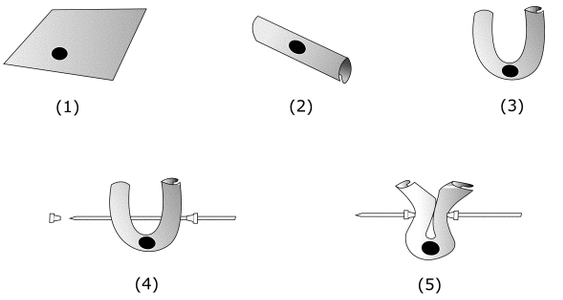

Fig. 1

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*—•The percentage of the labeled amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at the times given conforms to *Acceptance Table 2*.•$_{2}$

Time (hours)	Amount dissolved
2	between 20% and 35%
8	between 40% and 65%
14	between 60% and 90%
24	not less than 85%

•(Official April 1, 2006)•$_{2}$

Quinidine Gluconate Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•$_{2}$ with which the product complies.

•(Official April 1, 2006)•$_{2}$

Change to read:

•**Dissolution** ⟨711⟩—•$_{2}$

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1*.•$_{2}$

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 L 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, 2, 4, and 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 *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 2*.•$_{2}$

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 *Dissolution Test 4*.•$_{2}$

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 2*.•$_{2}$

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 *Dissolution Test 5*.•$_{2}$

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* using 8-mesh sinker baskets.*

Times: 1, 2, and 4 hours.

* A suitable sinker is available from VanKel, www.varianinc.com, catalog number 12-3062.

Tolerances—The percentages of the labeled amount of quinidine gluconate dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

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

•(Official April 1, 2006)•$_{2}$

Quinidine Sulfate Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•$_{2}$ with which the product complies.

•(Official April 1, 2006)•$_{2}$

Change to read:

•**Dissolution** ⟨711⟩—•$_{2}$

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.*•$_{2}$

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 4, and 12 hours.

Procedure—Using filtered portions of the solution under test, diluted with 0.1 N hydrochloric acid if necessary, determine the amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 248 nm by comparison with a Standard solution having a known concentration of USP Quinidine Sulfate RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 20% and 50%
4	between 43% and 73%
12	not less than 70%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•$_{2}$

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 4, and 12 hours.

Procedure—Proceed as directed for *Test 1.*

Tolerances—The percentages of the labeled amount of $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 10% and 35%
4	between 30% and 55%
12	not less than 75%

•(Official April 1, 2006)•$_{2}$

Sulfasalazine Delayed-Release Tablets

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•$_{2}$

ACID STAGE—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 120 minutes.

At the end of 120 minutes, determine the amount of $C_{18}H_{14}N_4O_5S$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, isopropanol, acetonitrile, and glacial acetic acid (22 : 11 : 7 : 0.4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Sulfasalazine RS in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 55.6 µg per mL.

Test solution—Pass about 7 mL of the solution under test through a membrane filter having a 0.45-µm porosity.

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 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time for sulfasalazine is about 7.7 minutes; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject a volume (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the peak responses. Calculate the percentage of $C_{18}H_{14}N_4O_5S$ dissolved by the formula:

$$(900C_S / LC)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Sulfasalazine RS in the *Standard solution; LC* is the label claim, in mg; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not more than 10% of the labeled amount of $C_{18}H_{14}N_4O_5S$ is dissolved in 120 minutes.

BUFFER STAGE—

Medium: pH 7.5 phosphate buffer; 900 mL.

Apparatus 1: 100 rpm.

Time: 60 minutes.

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At the end of 60 minutes, determine the amount of $C_{18}H_{14}N_4O_5S$ dissolved by employing the chromatographic method as described under *Acid stage*.

Tolerances—Not less than 85% *(Q)* of the labeled amount of $C_{18}H_{14}N_4O_5S$ is dissolved in 60 minutes.

•(Official April 1, 2006)•2

Theophylline Extended-Release Capsules

Change to read:

Labeling—The labeling indicates whether the product is intended for dosing every 12 or 24 hours, and states with which in vitro •*Dissolution Test*•2 the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2[NOTE—The following tests, which were assigned numbers chronologically, are placed in groups corresponding to product dosing intervals. Thus, individual tests do not necessarily appear in numerical order.]

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1.* Proceed as directed for *Method B* under *Apparatus 1 and 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

Medium: pH 1.2 simulated gastric fluid (without pepsin) for the first hour; pH 6.0 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Procedure—Determine the amount of $C_7H_8N_4O_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 271 nm on filtered portions of the solution under test, diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Theophylline RS in the same *Medium.*

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 3% and 15%
2	between 20% and 40%
4	between 50% and 75%
6	between 65% and 100%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2.*•2

pH 4.5 Phosphate buffer—Dissolve 6.8 g of monobasic potassium phosphate in 750 mL of water, mix, and dilute with water to 1000 mL. Adjust with either 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 4.5 ± 0.05.

Medium: pH 4.5 Phosphate buffer; 900 mL.

Apparatus 2: 75 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 30%
2	between 30% and 55%
4	between 55% and 80%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3.*•2 Proceed as directed for *Method B* under •*Apparatus 1 and 2, Delayed-Release Dosage Forms,* except to use *Acceptance Table 2.*•2

Medium: pH 1.2 simulated gastric fluid (without pepsin) for 1 hour; pH 7.5 simulated intestinal fluid (without enzyme); 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 1% and 17%
2	between 30% and 60%
3	between 50% and 90%
4	not less than 65%
7	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 4.*•2 Proceed as directed for *Method A* under •*Apparatus 1 and 2, Delayed-Release Dosage Forms*, except to use *Acceptance Table 2.*•2

Medium: pH 3.0 phosphate buffer prepared by adjusting 0.05 M potassium phosphate buffer with phosphoric acid to a pH of 3.0 ± 0.05, for the first 3½ hours, followed by the addition of 5.3 M sodium hydroxide to adjust to a pH of 7.4 ± 0.05; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 13% and 38%
2	between 25% and 50%
3.5	between 37% and 65%
5	between 85% and 115%

TEST 5—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 5.*•2

Medium, *Apparatus*, and *Procedure*—Proceed as directed under *Test 4*.

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 10% and 30%
3.5	between 30% and 60%
5	between 50% and 80%
7	not less than 65%
10	not less than 80%

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TEST 7—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 7.*•$_{2}$

Phosphate buffer—Dissolve 40.8 g of monobasic potassium phosphate in 6 L of water, add 667 mg of octoxynol 9, mix, and adjust with dilute hydrochloric acid or sodium hydroxide to a pH of 4.5.

Medium: Phosphate buffer; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1*.

Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 10% and 40%
2	between 35% and 70%
4	between 60% and 90%
8	not less than 85%

TEST 8—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 8.*•$_{2}$

Medium: pH 7.5 simulated intestinal fluid (without enzyme); 900 mL.

Apparatus 1: 100 rpm.

Procedure—Proceed as directed under *Test 1*.

Times and *Tolerances*—The percentages of labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 3% and 30%
2	between 15% and 50%
4	between 45% and 80%
6	not less than 70%
8	not less than 85%

TEST 9—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 9.*•$_{2}$

Medium 1: 0.1 N hydrochloric acid; 900 mL.

Medium 2: simulated intestinal fluid (without enzyme); 900 mL.

Apparatus 1: 50 rpm.

Determine the amount of theophylline dissolved at the times specified, using *Medium 1* for the first hour and *Medium 2* for the next five hours.

Procedure—Proceed as directed under *Test 1*.

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 5% and 15%
2	between 25% and 45%
3	between 50% and 65%
4	not less than 70%
6	not less than 85%

TEST 10—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 10.*•$_{2}$ Proceed as directed for *Test 3*.

Times and *Tolerances*—•The percentage of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times given conforms to *Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 6% and 27%
2	between 25% and 50%
4	between 65% and 85%
8	not less than 80%

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

TEST 6—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 6.*•$_{2}$

Medium: 0.05 M pH 6.6 phosphate buffer (see *Buffer Solutions* in the section *Reagents*, *Indicators*, *and Solutions*); 1000 mL.

Apparatus 1: 100 rpm.

Procedure—Proceed as directed under *Test 1*.

Times and *Tolerances*—The percentages of the labeled amount of $C_7H_8N_4O_2$ dissolved at the times specified conform to •*Acceptance Table 2.*•$_{2}$

Time (hours)	Amount dissolved
1	between 5% and 15%
2	between 12% and 30%
4	between 25% and 50%
5	between 30% and 60%
8	between 55% and 75%

•(Official April 1, 2006)•$_{2}$

Trihexyphenidyl Hydrochloride Extended-Release Capsules

Change to read:

•**Dissolution** ⟨711⟩—•$_{2}$

Medium: water; 500 mL.

Apparatus 1: 100 rpm.

Times: 3, 6, and 12 hours.

Determine the amount of $C_{20}H_{31}NO \cdot HCl$ dissolved, using the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and triethylamine (920 : 80 : 0.2), and adjust with phosphoric acid to a pH of 4.0.

Standard solution—Dissolve an accurately weighed quantity of USP Trihexyphenidyl Hydrochloride RS in water, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about 5 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 8.3-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 for the trihexyphenidyl peak is not more than 2.8, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Dilute the *Standard solution* and the solution under test with acetonitrile (1 : 1). Separately inject equal volumes (about 20 µL) of these solutions into the chromatograph, record the chromatograms, and measure the responses for trihexyphenidyl. Calculate the percentage of the labeled amount of $C_{20}H_{31}NO \cdot HCl$ dissolved.

Tolerances—The percentages of the labeled amount of $C_{20}H_{31}NO \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2*.•2

Time (hours)	Amount dissolved
3	between 20% and 50%
6	between 40% and 70%
12	not less than 70%

•(Official April 1, 2006)•2

Verapamil Hydrochloride Extended-Release Tablets

Change to read:

Labeling—The labeling indicates the •*Dissolution Test*•2 with which the product complies.

•(Official April 1, 2006)•2

Change to read:

•**Dissolution** ⟨711⟩—•2

TEST 1—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 1*. Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms*.•2

Acid stage—Using 900 mL of simulated gastric fluid TS (without enzyme), conduct this stage of the test for 1 hour.

Buffer stage—Using 900 mL of simulated intestinal fluid TS (without enzyme), conduct this stage of the test for 7 hours.

Apparatus 2: 50 rpm.

Times: Acid stage—1 hour; *Buffer stage*—2, 3.5, 5, and 8 hours.

Procedure—Wrap each Tablet in a wire helix to prevent the Tablets from floating. After 1 hour in the *Acid stage*, withdraw a specimen for analysis, and carefully transfer the dosage form, including the wire helix, to a vessel containing the *Buffer stage* medium, which has been previously warmed to 37 ± 0.5°. Filter a portion of the solution under test at each time interval, using a suitable glass microfiber filter paper. [NOTE—Use only filters that have been shown not to absorb verapamil.] Dilute, if necessary, the filtered portions of the solutions under test with water at the 1-hour interval and with 0.1 N hydrochloric acid at the 2-, 3.5-, 5-, and 8-hour intervals. Determine the amounts of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm, using 0.01 N hydrochloric acid as the blank, by comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in 0.01 N hydrochloric acid.

Tolerances—The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to •*Acceptance Table 2*.•2

FOR PRODUCTS LABELED TO CONTAIN 180 MG OR 240 MG:

Time (hours)	Amount dissolved
1	between 7% and 15%
2	between 16% and 30%
3.5	between 31% and 50%
5	between 51% and 75%
8	not less than 85%

FOR PRODUCTS LABELED TO CONTAIN 120 MG:

Time (hours)	Amount dissolved
1	between 10% and 21%
2	between 18% and 33%
3.5	between 35% and 60%
5	between 50% and 82%
8	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 2*.•2 Proceed as directed for *Test 1*, except that under *Procedure*, the Tablet is not required to be wrapped in a wire helix.

Times and *Tolerances*—•The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to *Acceptance Table 2*.•2

FOR PRODUCTS LABELED TO CONTAIN 240 MG:

Time (hours)	Amount dissolved
1	between 8% and 20%
2	between 15% and 35%
3.5	between 35% and 65%
5	between 55% and 85%
8	not less than 80%

FOR PRODUCTS LABELED TO CONTAIN 180 MG:

Time (hours)	Amount dissolved
1	between 10% and 25%
2	between 20% and 40%
3.5	between 40% and 75%
8	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 3*.•2 Proceed as directed for *Test 1*.

Times and *Tolerances*—•The percentage of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conforms to *Acceptance Table 2*.•2

Time (hours)	Amount dissolved
1	between 8% and 20%
2	between 15% and 35%
3.5	between 27% and 57%
5	between 45% and 75%
8	not less than 80%

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TEST 4—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 4.*•2

Phosphate buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water. Add 190 mL of 0.2 N sodium hydroxide in 400 mL of water, adjust with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1, dilute with water to 1000 mL, and mix.

Medium: *Phosphate buffer solution;* 50 mL.

Apparatus 7 •(see *Drug Release* ⟨724⟩):•2 20 cycles per minute.

Procedure—Scrape about 2 mm × 2 mm of the coating from the side edge of the tablet under test. Glue the system to a plastic rod sample holder at the area where the color has been removed. Attach each plastic sample holder to an arm of the apparatus, which reciprocates at an amplitude of about 2 cm and 15 to 30 cycles per minute. The tablet is continuously immersed in tubes containing 50 mL of *Medium* at 37°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium.* Remove the tubes after the last test interval, and allow them to cool to room temperature. Add 2.0 mL of 1.0 M phosphoric acid to each tube, and dilute with water to 50 mL. Stir and mix each tube thoroughly. Determine the amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ 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 *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in the same *Medium.*

Times and *Tolerances*—The percentages of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
3	not more than 10%
6	between 20% and 50%
9	between 52.5% and 82.5%
14	not less than 85%

TEST 5—If the product complies with this test, the labeling indicates that it meets •USP *Dissolution Test 5.*•2

Phosphate buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water. Add 190 mL of 0.2 N sodium hydroxide in 400 mL of water, adjust with 0.2 N sodium hydroxide to a pH of 7.5 ± 0.1, dilute with water to 1000 mL, and mix.

Medium: *Phosphate buffer solution;* 900 mL.

Apparatus 2: 50 rpm.

Procedure—Determine the amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ 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 *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Verapamil Hydrochloride RS in the same *Medium*.

Times and *Tolerances*—The percentages of the labeled amount of $C_{27}H_{38}N_2O_4 \cdot HCl$ dissolved at the times specified conform to •*Acceptance Table 2.*•2

Time (hours)	Amount dissolved
1	between 2% and 12%
2	between 10% and 25%
4	between 25% and 50%
8	not less than 80%

•(Official April 1, 2006)•2

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:

USP Bisoprolol Fumarate RS—•Dry portion at 60° for 3 hours before using. Protect from light. Keep container tightly closed.•2

Add the following:

•**USP Casticin RS**—Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from light.•2

Change to read:

USP Cephalexin RS—Do not dry before using. This is a monohydrate form of cephalexin. Keep container tightly closed. •For quantitative applications, determine the water content titrimetrically at the time of use.•2

Change to read:

USP Clemastine Fumarate RS—•Do not dry.•2 Keep container tightly closed. Protect from light. ••2

Change to read:

USP Diazepam RS—•Do not dry.•2 Keep container tightly closed. Protect from light.

Change to read:

USP Flurbiprofen RS—•Do not dry.•2 Keep container tightly closed.

Change to read:

USP Iodoquinol RS—•Do not dry.•2 Keep container tightly closed.

Change to read:

USP Letrozole Related Compound A RS **[**4,4′-(1*H*-1,3,4-triazol-1-ylmethylene)dibenzonitrile**]** ($C_{17}H_{11}N_5$ ✧ 285.31)—Do not dry. •Keep container tightly closed. Protect from light.•2

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Change to read:

USP Palmitic Acid RS—•Do not dry. Store in a refrigerator.•2 Keep container tightly closed.

Change to read:

USP β-Sitosterol RS—Do not dry. •For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic.•2

Change to read:

USP Stearic Acid RS—•Do not dry.•2 Keep container tightly closed.

Change to read:

USP Tamoxifen Citrate RS—•Do not dry. Store in a refrigerator.•2 Keep container tightly closed. Protect from light.

Change to read:

USP Zidovudine RS—Do not dry. ••2 Keep container tightly closed and protected from light. •Store in a refrigerator.•2

Physical Tests and Determinations

Change to read:

•⟨701⟩ DISINTEGRATION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national *USP* text, and therefore not part of the harmonized text, are marked with symbols (••) to specify this fact.

This test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. •Compliance with the limits on *Disintegration* stated in the individual monographs is required except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as extended-release dosage forms or delayed-release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.•

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plates, each 88 to 92 mm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained. The basket-rack assembly conforms to the dimensions found in *Figure 1*.

Disks—The use of disks is permitted only where specified or allowed •in the monograph. If specified in the individual monograph,• each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2 ± 0.1-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 ± 0.2 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 ± 0.1 mm, and its bottom edges lie at a depth of 1.6 ± 0.1 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified •in the individual monograph,• add a disk to each tube, and operate the apparatus as directed under *Procedure*. The disks conform to dimensions found in *Figure 1*[1]

[1] The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimension given in this chapter.

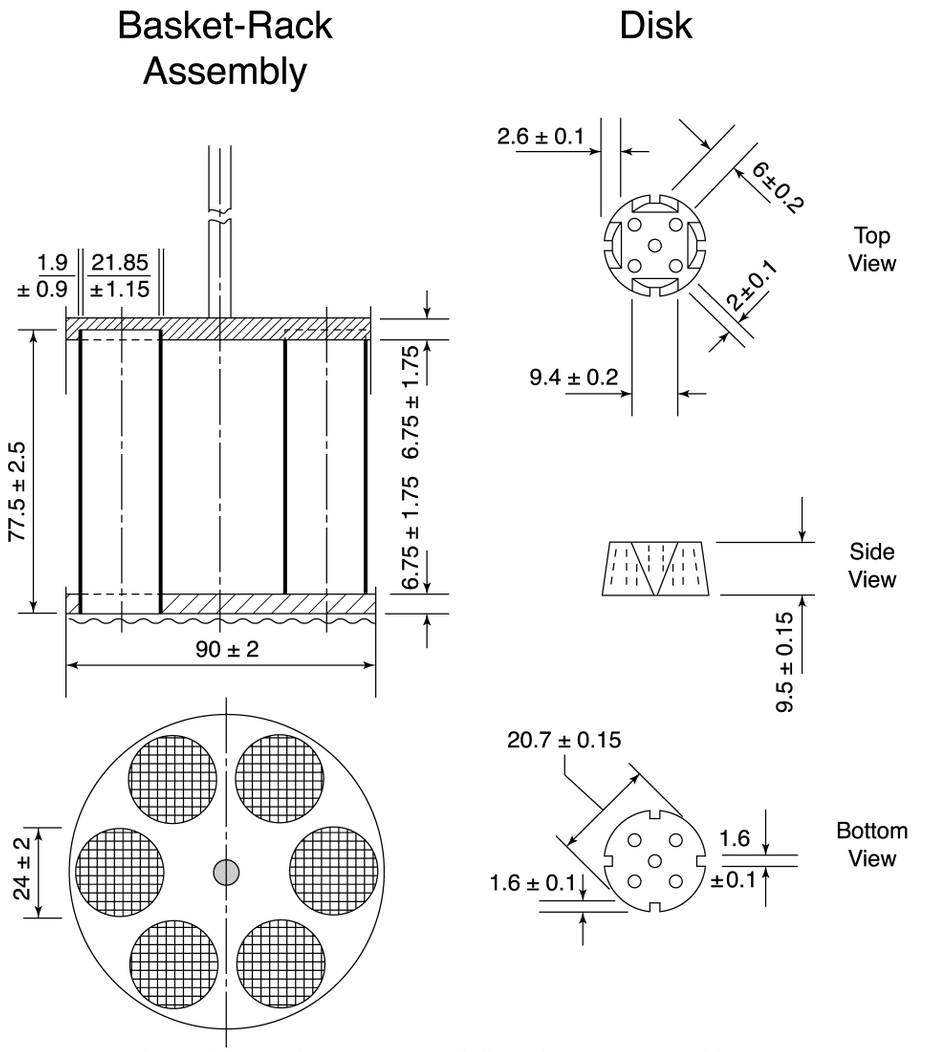


Fig. 1. Disintegration apparatus. (All dimensions are expressed in mm.)

PROCEDURE

◆**Uncoated Tablets**—◆Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus, using ◆water or◆ the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of the time limit specified ◆in the monograph,◆ lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested are disintegrated.

◆**Plain-Coated Tablets**—Apply the test for *Uncoated Tablets,* operating the apparatus for the time specified in the individual monograph.

Delayed-Release (Enteric-Coated) Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets.* At the end of the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-Rack Assembly,* to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.◆ ●[2]

(Official April 1, 2006)

Change to read:

●⟨711⟩ DISSOLUTION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the European Pharmacopoeia or the Japanese Pharmacopoeia may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (◆ ◆) to specify this fact.

This test is provided to determine compliance with the dissolution requirements ◆where stated in the individual monograph,◆ for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. ◆Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for *Delayed-Release Dosage Forms* is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

USP Reference Standards ⟨11⟩—*USP Chlorpheniramine Maleate Extended-Release Tablets RS (Drug Release Calibrator, Single Unit). USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS. (Dissolution Calibrator, Nondisintegrating).*◆

APPARATUS

Apparatus 1 (Basket Apparatus)

The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or heated by a suitable device such as a heating jacket. The water bath or heating device permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. 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 smoothly rotating stirring element. An apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and ◆with one of the following dimensions and capacities: for a nominal◆ capacity of 1 L, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; ◆for a nominal capacity of 2 L, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 L, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm◆. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the specified rate ◆given in the individual monograph,◆ within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316, or other inert material, to the specifications shown in *Figure 1.* A basket having a gold coating of about 0.0001 inch (2.5 μm) thick may be used. A dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

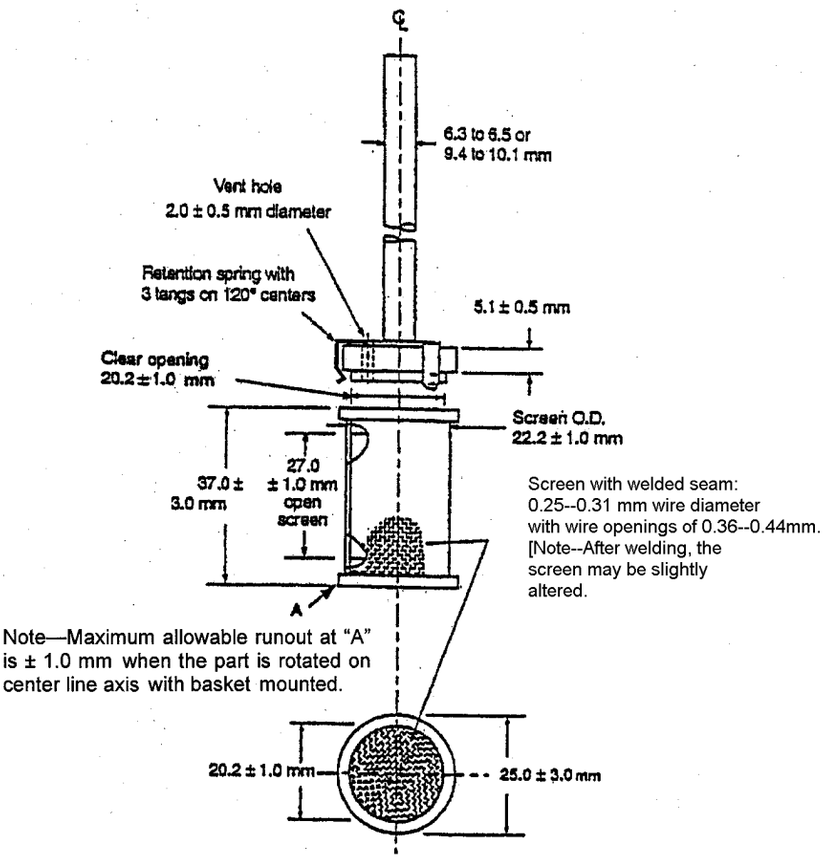


Fig. 1. Basket Stirring Element

Apparatus 2 (Paddle Apparatus)

Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in *Figure 2.* The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in *Figure 2a*. Other validated sinker devices may be used.

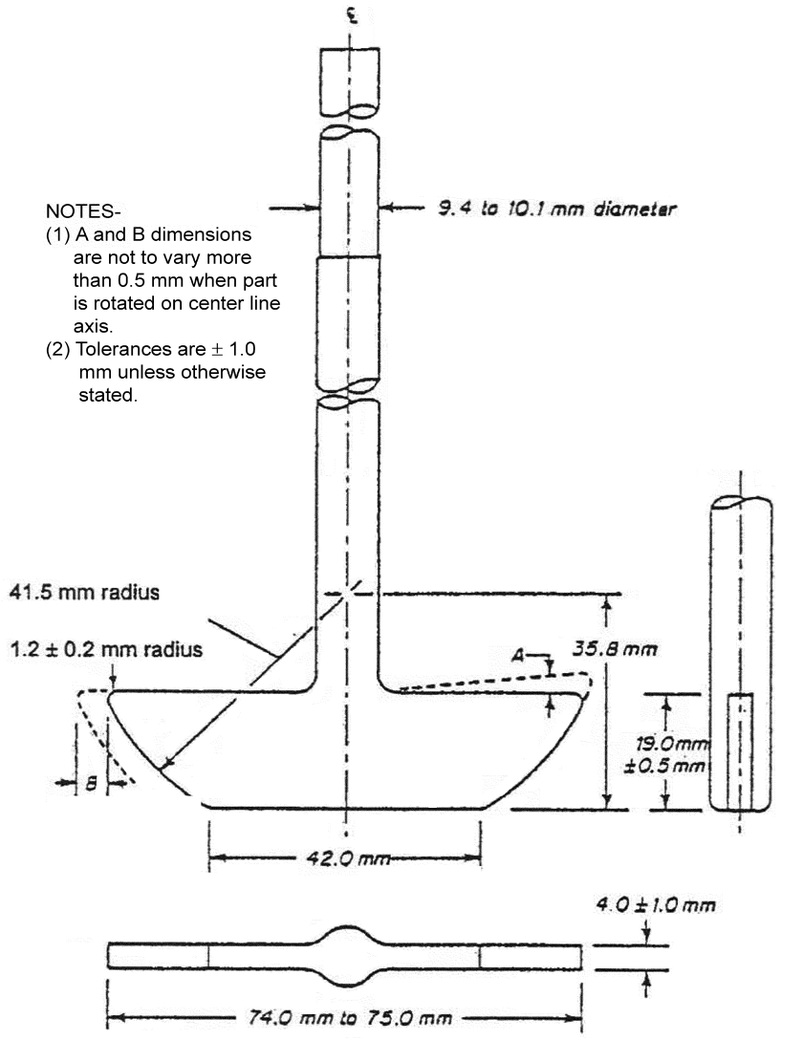


Fig. 2. Paddle Stirring Element

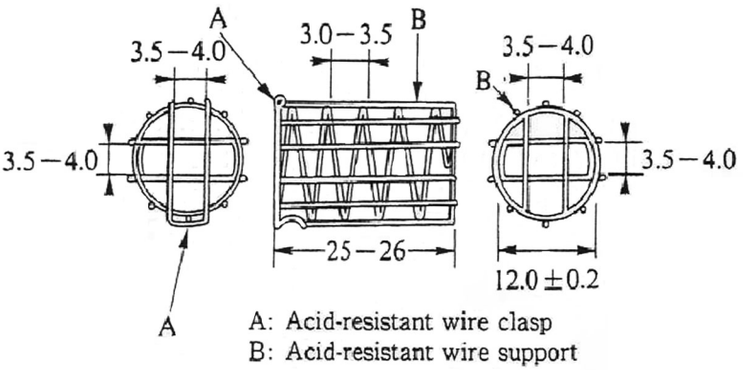


Fig. 2a. Alternative sinker. All dimensions expressed in mm.

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; inert fittings (stainless steel type 316 or other suitable material), 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 specified dip rate ◆given in the individual monograph◆ within ±5%. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The vessels are provided with an evaporation cap that remains in place for the duration of the test. The components conform to the dimensions shown in *Figure 3* unless otherwise specified ◆in the individual monograph◆.

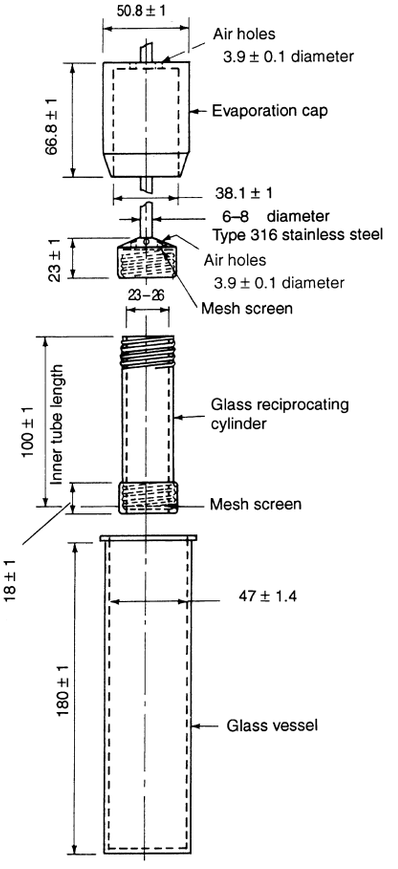


Fig. 3. Apparatus 3 (reciprocating cylinder)

Apparatus 4 (Flow-Through Cell)

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°. Use the specified cell size ◆as given in the individual monograph◆.

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 deliver a constant flow ($\pm$5% of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 $\pm$ 10 pulses per minute.

The flow-through cell (see *Figures 4* and *5*), 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 4* and *5*) 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 $\pm$ 0.5°.

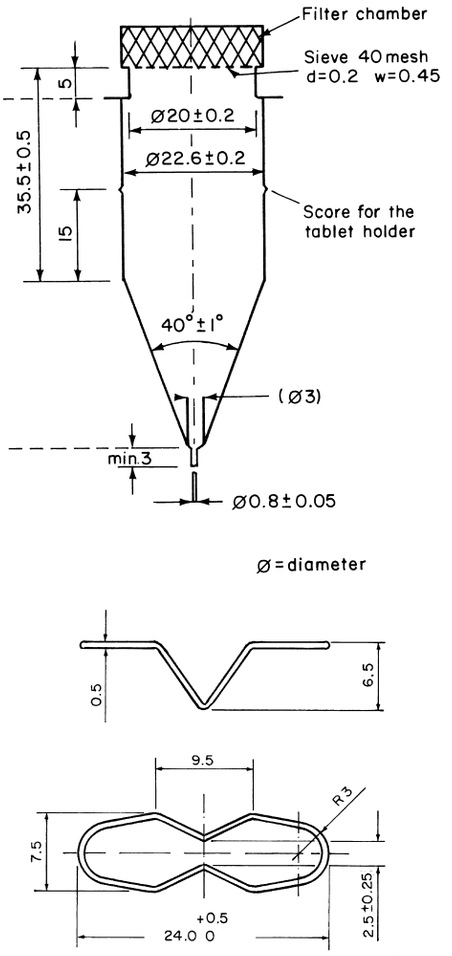


Fig. 4. Large cell for tablets and capsules (top) Tablet holder for the large cell (bottom) (All measurements are expressed in mm unless noted otherwise.)

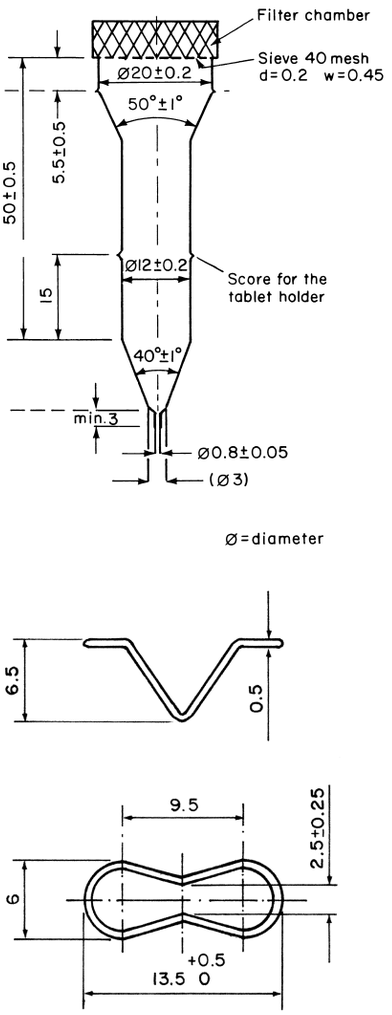


Fig. 5. Small cell for tablets and capsules (top) Tablet holder for the small cell (bottom) (All mesurements are expressed in mm unless noted otherwise.)

The apparatus uses a clamp mechanism and two O-rings to assemble the cell. 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 suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections.

APPARATUS SUITABILITY

The determination of suitability of a test assembly to perform dissolution testing must include conformance to the dimensions and tolerances of the apparatus as given above. In addition, critical test parameters that have to be monitored periodically during use include volume and temperature of the *Dissolution Medium,* rotation speed (*Apparatus 1* and *Apparatus 2*), dip rate (*Apparatus 3*), and flow rate of medium (*Apparatus 4*).

Determine the acceptable performance of the dissolution test assembly periodically. ◆The suitability for the individual apparatus is demonstrated by the *Apparatus Suitability Test*.

Apparatus Suitability Test, Apparatus 1 and 2—Individually test 1 tablet of the USP Dissolution Calibrator, Disintegrating Type and 1 tablet of USP Dissolution Calibrator, Nondisintegrating Type, according to the operating 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.

Apparatus Suitability Test, Apparatus 3—Individually test 1 tablet of the USP Drug Release Tablets (Single Unit) according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate.

Apparatus Suitability Test, Apparatus 4—[To come.]◆

PROCEDURE

Apparatus 1 and Apparatus 2

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the specified apparatus ◆given in the individual monograph,◆ assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate ◆given in the individual monograph◆. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis ◆as directed in the individual monograph◆ using a suitable assay method.[3] Repeat the test with additional dosage form units.

If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary.

Dissolution Medium—A suitable dissolution medium is used. Use the solvent specified ◆in the individual monograph.◆The volume specified refers to measurements made between 20° and 25°. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH ◆given in the individual monograph.◆ [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.[4]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms*.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms*.

Time—The test-time points, generally three, are expressed in hours.

DELAYED-RELEASE DOSAGE FORMS

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

Use *Method A* or *Method B* and the apparatus specified ◆in the individual monograph.◆ All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate ◆given in the monograph◆.

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.]

With the apparatus operating at the rate specified ◆in the monograph,◆ add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for the minimum amount dissolved is met at an earlier time.◆

Method B—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified ◆in the monograph◆. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph◆.

BUFFER STAGE—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3 : 1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.]

[3] Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.◆

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

IMMEDIATE-RELEASE DOSAGE FORMS

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 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 3*.

Dissolution Medium—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

DELAYED-RELEASE DOSAGE FORMS

Proceed as described for *Delayed-Release Dosage Forms, Method B* under *Apparatus 1 and Apparatus 2* using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Apparatus 4 (Flow-Through Cell)

IMMEDIATE-RELEASE DOSAGE FORMS

Place the glass beads into the cell specified ◆in the monograph◆. Place 1 dosage 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2,* using the specified media.

Time—Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

INTERPRETATION

Immediate-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 1*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient ◆specified in the individual monograph,◆expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in *Acceptance Table 1* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q – 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

Extended-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. 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 spec-

Interim Revision Announcement

ified fractional dosing interval. Where more than one range is specified ◆in the individual monograph◆, the acceptance criteria apply individually to each range.

Acceptance Table 2

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.

Delayed-Release Dosage Forms

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA.

Acid Stage—Unless otherwise specified ◆in the individual monograph◆, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 3

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—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 4*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 4* is 75% dissolved unless otherwise specified ◆in the individual monograph◆. The quantity, Q,◆specified in the individual monograph◆ is the total amount of active ingredient dissolved in both the *Acid* and *Buffer Stages*, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in *Acceptance Table 4* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q – 15%.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

●2

(Official April 1, 2006)

Change to read:

●⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at the temperature specified in the monograph or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

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 1*).

[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 SandwichTM from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

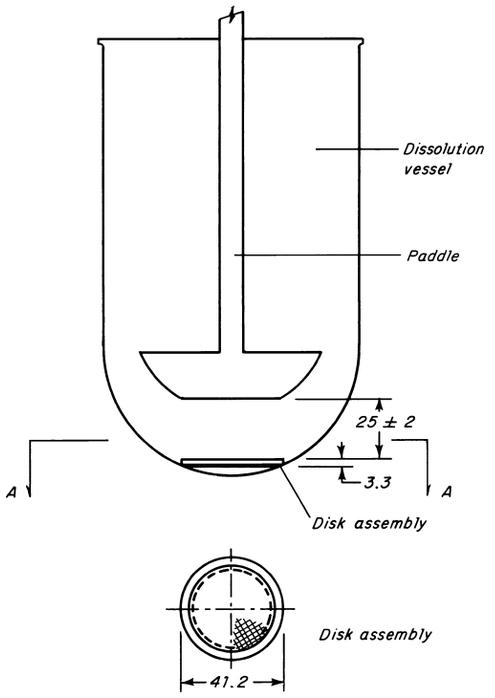


Fig. 1. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

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 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 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 1

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 2*. 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.

[3] Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, 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.

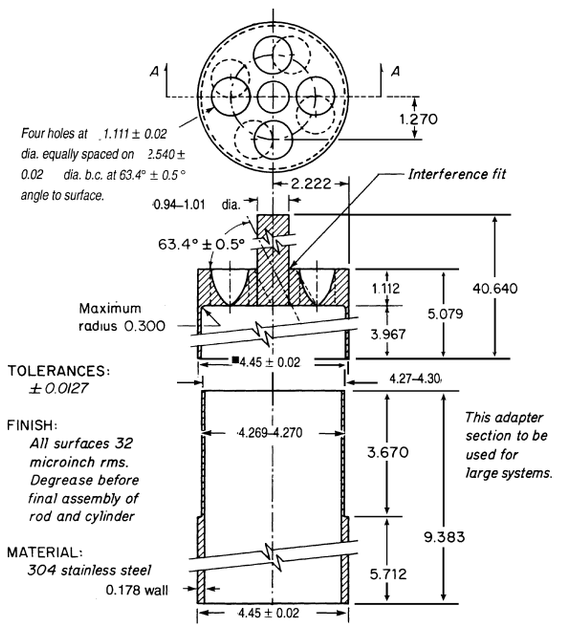


Fig. 2. Cylinder Stirring Element.[5]
(All measurements are expressed in cm unless noted otherwise.)

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 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 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7 (Reciprocating Holder)

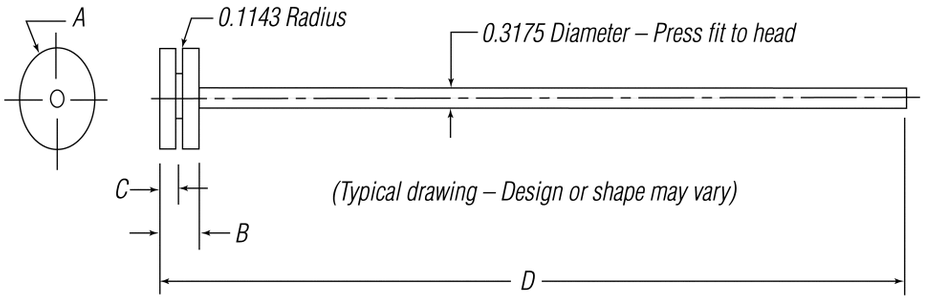
NOTE—This apparatus may also be specified for use with a variety of dosage forms.

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 3*[7] and *Figures 4a–4d*). 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.

[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.

[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.



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. 3. Reciprocating Disk Sample Holder.[7]

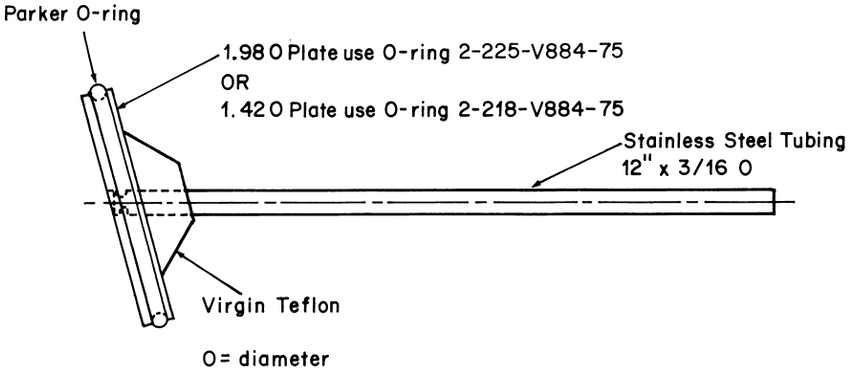


Fig. 4a. Transdermal System Holder—Angled Disk.

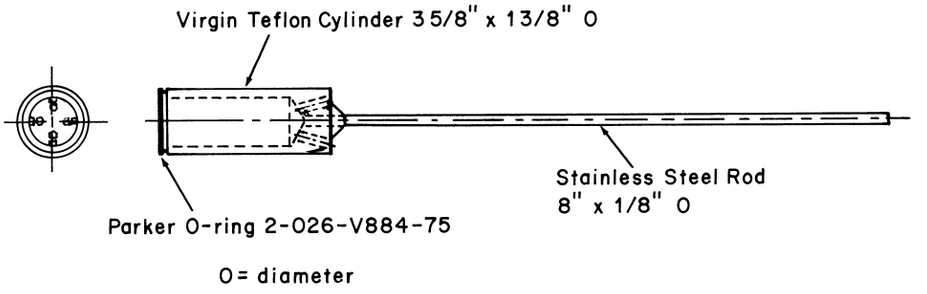


Fig. 4b. Transdermal System Holder—Cylinder.

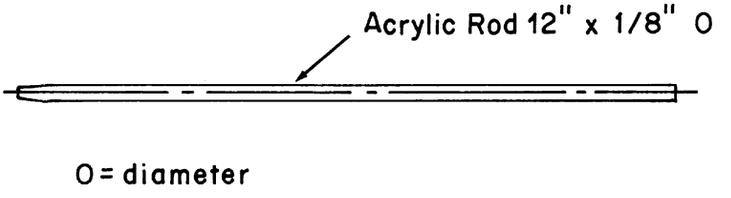
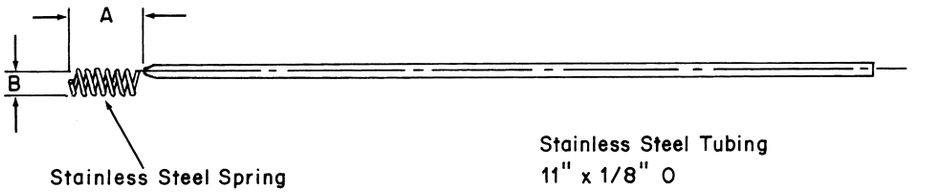


Fig. 4c. Oral Extended-Release Tablet Holder—Rod, Pointed for Gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O= diameter

Fig. 4d. 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 2* under *Dissolution* ⟨711⟩ for coated tablet drug delivery systems, to *Acceptance Table 1* 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.●2

(Official April 1, 2006)

ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
123	*Aminocaproic Acid*	*Assay*	Line 6 under *Procedure:* Change "quantity, in mg," to: quantity, in g,
297	*Bupropion Hydrochloride Extended-Release Tablets*	*Identification A*	Line 4 under *Test specimen:* Change "790 cm^{-1}" to: 740 cm^{-1}
402	*Ceftazidime for Injection*	*Limit of pyridine*	Line 3 under *Test solution:* Change "promptly add 50 mL of *pH 7 buffer* to volume," to: promptly add *pH 7 buffer* to volume,
464	*Cholestyramine Resin*	*Dialyzable quaternary amines*	Line 1 under *pH 9.2 Buffer:* Change "sodium borate" to: sodium borate decahydrate
			Line 2 under *Bromothymol blue solution:* Change "sodium carbonate decahydrate" to: sodium carbonate
488	*Clavulanate Potassium*	*Assay*	Line 2 under *Standard preparation:* Change "USP Clavulanate in water" to: USP Clavulanate Lithium RS in water
		Limit of aliphatic amines	Table under *Chromatographic system,* line 2, column 3: Change "35–50" to: 35–150
515	*Clonidine Transdermal System*	*Identification A*	Line 22 under *Sample preparation:* Change "wavelength region of 3500 to 3600 cm^{-1}" to: wavelength region of 3500 to 600 cm^{-1}
640	*Digitalis*	*Assay*	Line 9 under *Calculation of potency:* Change "Compute the log confidence interval" to: Compute the confidence interval
726	*Trace Elements Injection*	*Labeling*	Line 12: Change "chromic chloride ($CrCl_2$)," to: chromic chloride ($CrCl_3$),
760	*Erythromycin Ointment*	*Assay*	Lines 4 and 5 under *Chromatographic system:* Change "L52" to: L50
1191	*Mecamylamine Hydrochloride*	*Assay*	Line 12 under *Chromatographic system:* Change "is not less" to: is not more

ERRATA *(Continued)*

Page	Title	Section	Description
2430	⟨736⟩ *Mass Spectrometry*	*Ionization Techniques*	Line 7 under *Electron Impact:* Change

$$e^- + M - M^+ \bullet + 2e^-.$$

to:

$$e^- + M \rightarrow M^+ \bullet + 2e^-.$$

Line 13 under *Chemical Ionization:* Change

$$CH_5^+ + M - MH^+ + CH_4.$$

to:

$$CH_5^+ + M \rightarrow MH^+ + CH_4.$$

Line 4 under *Fast Atom Bombardment:* Change

$$Xe \rightarrow Xe^+ + e^-$$
$$Xe^+ + Xe \rightarrow Xe + Xe^+,$$

to:

$$Xe \rightarrow Xe^+ + e^-$$
$$\underrightarrow{Xe}^+ + Xe \rightarrow \underrightarrow{Xe} + Xe^+,$$

Interim Revision Announcement

ERRATA *(Continued)*

Page	Title	Section	Description
2712	⟨1160⟩ *Pharmaceutical Calculations in Prescription Compounding*	*Percentage Concentrations*	Third equation: Change $\text{Weight in volume percent (w/v)} = \frac{\text{Weight of solute (in g)}}{\text{Weight of solution (in mL)}} \times 100\%$ to: $\text{Weight in volume percent (w/v)} = \frac{\text{Weight of solute (in g)}}{\text{Volume of solution (in mL)}} \times 100\%$
3088	*Pregelatinized Starch*	*Microbial limits*	Line 4: Change "1000 cfu per g" to: 100 cfu per g

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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24*; and

■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*, ■2S (*USP 28*) indicates that the proposed revision is slated for the *Second Supplement to USP 28*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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.

MONOGRAPHS (USP)

BRIEFING

Amphetamine Sulfate, *USP 28* page 148 and page 807 of *PF* 30(3) [May–June 2004]. It is proposed to replace the current *Assay* method by the same procedure used in the *Assay* under *Dextroamphetamine Sulfate.*

(PA3: R. Ravichandran) RTS—41946-1

Change to read:

Identification—

A: Dissolve about 100 mg in 5 mL of water, add 5 mL of 1 N sodium hydroxide, cool to about 10°, add 1 mL of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, insert the stopper, and shake for 3 minutes. Filter the precipitate, wash with about 10 mL of cold water, and recrystallize from diluted alcohol: the crystals of the benzoyl derivative of amphetamine so obtained, after drying at 80° for ~~2 hours,~~

■3 hours,■1S *(USP28)*
melt between 131° and 135°, the procedure for *Class I* being used (see *Melting Range or Temperature* ⟨741⟩).

B: A solution (1 in 10) responds to the tests for *Sulfate* ⟨191⟩.

Change to read:

Assay—

~~*Standard preparation*—Prepare as directed under *Amphetamine Assay* ⟨331⟩.~~

~~*Assay preparation*—Dissolve about 125 mg of Amphetamine Sulfate, previously dried and accurately weighed, in 25 mL of hydrochloric acid solution (1 in 100) in a 50-mL volumetric flask, dilute with the solvent to volume, and mix. Pipet 2.0 mL of the solution into a 100-mL beaker containing 3 g of purified siliceous earth, and mix until a fluffy mixture is obtained.~~

~~*Procedure*—Proceed as directed under *Amphetamine Assay* ⟨331⟩. Calculate the quantity, in mg, of $(C_9H_{13}N)_2 \cdot H_2SO_4$ in the portion of Amphetamine Sulfate taken by the formula:~~

$$0.25C[(A_{test} - A_{blank})/(A_{std} - A_{blank})],$$

~~in which *C* is the concentration, in µg per mL, of USP Dextroamphetamine Sulfate RS in the *Standard preparation*, and the other terms are as defined therein.~~

▲Dissolve about 500 mg of Amphetamine Sulfate, accurately weighed, in 50 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 36.85 mg of $(C_9H_{13}N)_2 \cdot H_2SO_4$.▲*USP29*

BRIEFING

Betamethasone Acetate, *USP 28* page 245. It is proposed to change the visualization reagent in *Identification* test *B* to 10% sulfuric acid in alcohol to reduce the hazard to the analyst.

(PA1: C. Anthony) RTS—42253-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—
Test solution: 0.5 mg per mL in dehydrated alcohol.
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)~~

▲10% sulfuric acid in alcohol▲*USP29*
and heating on a hot plate or under a lamp until spots appear.

BRIEFING

Bupropion Hydrochloride, *USP 28* page 296; **Bupropion Hydrochloride Extended-Release Tablets,** *USP 28* page 297, page 1562 of the *Fifth Interim Revision Announcement to USP 27–NF 22,* and in the *IRA* of this issue of *PF*. It is proposed to change the name of the test for *Chromatographic purity* to the test for *Related compounds* and to include the name of the impurities quantified in the *Procedure* under *Related compounds, Test 2* to facilitate the analysis of this compound. In addition, the formula to quantify the related compounds is modified according to the proposed method originally submitted. It is also proposed to change the TLC monitoring wavelength from 254 nm to 235 nm in *Related Com-*

In-Process Revision

pounds Test 1 to improve the sensitivity of the detection and quantification of *m*-chlorobenzoic acid. Other editorial changes have been made.

(PA3: S. Salado) RTS—41266-2

Change to read:

~~**Chromatographic purity**~~

▲Related compounds—▲*USP29*

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.

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.~~

▲4 µL.▲*USP29*

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.~~

▲235 nm.▲*USP29*

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—

▲*Diluent, 0.025 M Phosphate buffer, 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.*▲*USP29*

Procedure—Using the chromatograms obtained in the *Assay,* calculate the percentage of each impurity in the portion of Bupropion Hydrochloride taken by the formula:

~~$100F(r_i/r_s)$,~~

▲$5000(C/W)F(r_i/r_S)$,▲*USP29*

in which

▲C is the concentration, in mg per mL, of USP Bupropion Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of sample take to prepare the *Test solution;*▲*USP29*

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;*~~

▲*Test solution;*▲*USP29*

and r_S is the peak response for bupropion hydrochloride obtained from the ~~*Standard preparation.*~~

▲*Standard solution.*▲*USP29*

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~~	~~—~~	~~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.~~

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▲

Compound Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
2-(*tert*-Butylamino)propiophenone hydrochloride	about 0.38	0.68	0.5
1-(3-Chlorophenyl)-1,2-propanedione	about 0.58	0.96	0.2
2-(*tert*-Butylamino)-2′-chloropropiophenone hydrochloride	about 0.71	2.22	0.1
3′-Chloropropiophenone	about 0.78	0.82	0.1
Bupropion hydrochloride related compound A	about 0.92	0.73	0.2
Bupropion	1.0	—	—
Bupropion hydrochloride related compound B	about 1.14	—	0.2*
2-Bromo-3′-chloropropiophenone	about 1.63	1.13	0.1
2-(*tert*-Butylamino)-3′,4′-chloropropiophenone hydrochloride	about 2.30	0.91	0.2
2-(*tert*-Butylamino)-3′,5′-chloropropiophenone hydrochloride	about 2.74	1.45	0.2
Unknown	all other peaks	1.00	0.1, individual

* 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.* ▲*USP29*

In-Process Revision

BRIEFING

Bupropion Hydrochloride Extended-Release Tablets, *USP 28* page 297, page 1562 of the *Fifth Interim Revision Announcement to USP 27–NF 22,* and in the *IRA* of this issue of *PF*—See briefing under *Bupropion Hydrochloride*. It is proposed to quantify all of the impurities using the *Standard preparation* as directed in the *Assay.* Reference Standards that are no longer needed are deleted.

(PA3: R. Ravichandran) RTS—41266-1

Change to read:

USP Reference standards ⟨11⟩—*USP Bupropion Hydrochloride RS. USP Bupropion Hydrochloride Related Compound C RS.* ~~*USP Bupropion Hydrochloride Related Compound D RS. USP Bupropion Hydrochloride Related Compound E RS.*~~

▲▲*USP29*
USP Bupropion Hydrochloride Related Compound F RS.

Change to read:

Related compounds—

Solution A, Solution B, Mobile phase, System suitability solution 1, System suitability solution 2,

▲and *Chromatographic system*▲*USP29*
—Proceed as directed in the *Assay.*

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.~~

▲Use the *Standard preparation,* prepared as directed in the *Assay.*▲*USP29*

Test solution—Use the *Assay preparation.*

~~*Chromatographic system*—Proceed as directed in the *Assay,* except to use the *Standard solution* instead of the *Standard preparation.*~~

▲▲*USP29*
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~~	~~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~~

▲Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(C/D)F(r_i/r_S),$$

in which *C* is the concentration, in mg per mL, of bupropion hydrochloride in the *Standard solution; F* is the relative response factor for each impurity (see the accompanying table); *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; 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.

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Compound	Relative Retention Time	*F*	Limit (%) 100 mg or less	Limit (%) 150 mg or greater
2-Amino-1-(3-chlorophenyl)-1-propanone	about 0.38	0.80	0.3	0.3
(3*S*,5*S*,6*S*)-6-(3-Chlorophenyl)-6-hydroxy-5-methyl-3	about 0.56	0.86	1.0	1.5
Thiomorpholine-carboxylic acid	about 0.78	0.88	0.5	0.4
Bupropion	1.0	—	—	—
Bupropion related compound F	about 1.71	0.55	1.2	2.3
Bupropion related compound C	about 1.75	0.59	0.3	0.3
m-Chlorobenzoic acid	about 1.80	0.24	0.3	0.3
Bupropion related compound E	about 2.25	1.00	0.4	0.4
Any unspecified impurity	—	1.00	0.2	0.2
Total impurities	—	—	3.2	3.3

▲*USP29*

BRIEFING

Calcitonin Salmon, page 1169 of *PF* 30(4) [July–Aug. 2004]. On the basis of comments received, it is proposed to allow other methods besides *Method 1* under *Biotechnology-Derived Articles—Tests* ⟨1047⟩ to be used to perform the test for *Amino acid profile.* It is also proposed to lower the amount of material used to perform the test for *Microbial limits.*

(BNT: L. Callahan) RTS—42086-1

Add the following:

▲Calcitonin Salmon

$C_{145}H_{240}N_{44}O_{48}S_2$ 3432 daltons [*47931-85-1*].

» Calcitonin Salmon is a synthetic polypeptide that has the same sequence as that of the hormone-regulating calcium metabolism secreted by the ultimobranchial gland of salmon. It lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid–free and dried basis.

NOTE—1 mg of acetic acid–free, anhydrous Calcitonin Salmon is equivalent to 6000 USP Calcitonin Salmon Units.

Packaging and storage—Preserve in tight containers. Store protected from light in a refrigerator.

Labeling—The labeling states that the material is synthetic.

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USP Reference standards ⟨**11**⟩—*USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS* (*N*-acetyl-cys[1]-calcitonin). *USP Endotoxin RS.*

Identification—

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

B: The UV absorption spectrum of a 0.1% solution (based on free peptide) in 0.01 N hydrochloric acid exhibits a minima and a maxima at the same wavelengths as those of a similar solution of USP Calcitonin Salmon RS, concomitantly measured. The absorbance at approximately 275 nm (maxima) is about 0.40 to 0.55, and the ratio of the absorbance at 275 nm (maxima) and 254 nm (minima) is between 1.6 and 2.5.

Amino acid profile (see *Amino Acid Analysis ~~Method 1,~~* under *Biotechnology-Derived Articles—Tests* ⟨1047⟩)—[NOTE—The concentration of amino acids in the *Internal standard solution,* the *Standard amino acid solution,* and the *Standard solution* and the amount of material used to prepare the *Test solution* can be adjusted depending on the method used for amino acid analysis. The concentrations given are based on analysis using *Method 1.*]

Internal standard solution—Prepare a 1 mM solution of γ-aminobutyric acid.

Standard amino acid solution—Prepare a mixture containing equimolar amounts of ammonia and the L form of lysine, histidine, arginine, aspartic acid, threonine, serine, proline, valine, glutamic acid, glycine, leucine, and tyrosine, together with half the equimolar amount of L-cystine, in 0.1 M hydrochloric acid. The final concentration is about 2.5 mM for each amino acid.

Standard solution—Transfer 5 mL of the *Internal standard solution* and 2 mL of the *Standard amino acid solution* into a 50-mL volumetric flask, and dilute with 0.1 M hydrochloric acid to volume.

Test solution—Place about 1.5 mg of an accurately weighed quantity of Calcitonin Salmon into a heavy-wall ignition tube, add 1.0 mL of 6 N hydrochloric acid, allow to cool, immerse the lower half of the tube in a freezing mixture until the contents are frozen, evacuate to approximately 10 μM, purge with nitrogen (repeat the evacuation and nitrogen purge three times), and seal the tube while it is under a 10-μM vacuum. Heat for 16 hours at 110° to 115° in an air oven. Cool, open the tube, dry in a vacuum desiccator, remove the contents, and allow to cool to room temperature. Dissolve in 0.1 M hydrochloric acid, transfer to a 10-mL volumetric flask, add 1 mL of *Internal standard solution,* and dilute with 0.1 M hydrochloric acid to volume.

Procedure—Standardize the amino acid analyzer, using the *Standard solution.* Inject the *Test solution* into the amino acid analyzer, and determine the relative proportion of amino acids.

Calculation of amino acid profile—Express the content of each amino acid in moles, using an internal standard calibration technique. Calculate the relative proportions of the amino acids by taking as equivalent to 1 the sum divided by 20 of the number of moles of aspartic acid, glutamic acid, proline, glycine, valine, leucine, histidine, arginine, and lysine. For threonine and serine, perform the same calculation, and correct the concentrations for degradation by adding 5% and 10%, respectively, to their indicated results. The requirements are met if the values fall within the following limits: aspartic acid, 1.8 to 2.2; glutamic acid, 2.7 to 3.3; proline, 1.7 to 2.3; glycine, 2.7 to 3.3; valine, 0.9 to 1.1; leucine, 4.5

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to 5.3; histidine, 0.9 to 1.1; arginine, 0.9 to 1.1; lysine, 1.8 to 2.2; serine, 3.2 to 4.2; threonine, 4.2 to 5.2; tyrosine, 0.7 to 1.1; half cystine, 1.4 to 2.1.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 1000 USP Endotoxin Units per mg of calcitonin salmon.

Microbial limits ⟨61⟩**—**The test is performed on a portion of about 0.2 g, accurately weighed. The total aerobic microbial count does not exceed 100 cfu per g. It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

pH ⟨791⟩**:** between 4.0 and 6.0 in a 1% solution in carbon dioxide–free water.

Water, *Method Ic* ⟨921⟩**:** not more than 10%.

Heavy metals, *Method II* ⟨231⟩**:** 0.005%.

Limit of trifluoroacetic acid—[NOTE—Use deionized, degassed water where water is indicated.]

Solution A: water.

Solution B: 0.005 N sodium hydroxide.

Solution C: 0.1 N sodium hydroxide.

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

Chloride stock standard solution—Dissolve an accurately weighed quantity of sodium chloride in water to obtain a solution having a concentration of the chloride ion of about 0.1 mg per mL.

Trifluoroacetic acid stock standard solution—Dissolve an accurately weighed quantity of trifluoroacetic acid in water to obtain a solution having a concentration of trifluoroacetic acid of about 0.1 mg per mL.

Resolution solution—Pipet 0.2 mL of *Chloride stock standard solution* and 0.5 mL of *Trifluoroacetic acid stock standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution that contains 0.2 µg of chloride and 0.5 µg of trifluoroacetate per mL, respectively.

Standard solutions—Pipet 0.2 mL, 0.5 mL, 1.0 mL, and 2.0 mL of *Trifluoroacetic acid stock standard solution* into ordered 100-mL volumetric flasks. Dilute with water to volume and mix to obtain solutions that contain concentrations of about 0.2 µg, 0.5 µg, 1.0 µg, and 2.0 µg of trifluoroacetate per mL, respectively.

Test solution—Transfer about 10 mg of Calcitonin Salmon, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The ion chromatograph is equipped with a conductivity detector, a 4-mm × 5-cm anion-exchange guard column containing packing L31, a 4-mm × 25-cm anion-exchange analytical column containing packing L31, a high-capacity anion trap column in hydroxide form in the eluant line in front of the injection valve, and a micromembrane anion self-regenerating suppressor. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–2	90	10	0	isocratic
2–5	90→0	10→100	0	linear gradient
5–15	0	100→65	0→35	linear gradient
15–20	0→90	65→10	35→0	linear gradient

Chromatograph the *Resolution solution,* and record the peak responses as directed for the *Procedure:* the resolution, *R,* between the chloride peak and the trifluoroacetic acid peak is not less than 3; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area of peak responses. Plot the response of the trifluoroacetic acid peak in the *Standard solutions* versus the concentration of trifluoroacetic acid, and draw the straight line best fitting the plotted points. From the graphs so obtained, determine a concentration value, *C,* in µg per mL for trifluoroacetic acid. Calculate the quantity, in ppm, for trifluoroacetic acid in Calcitonin Salmon by the formula:

$$5000(C/W),$$

in which *W* is the weight in mg of Calcitonin Salmon taken to prepare the *Test solution:* not more than 200 ppm of trifluoroacetic acid is found.

Limit of residual solvents—

Standard stock solution—Prepare a solution containing about 300 µg of methanol, 40 µg of acetonitrile, 60 µg of methylene chloride, 500 µg of *tert*-butyl methyl ether, and 90 µg of dimethylformamide per mL of methyl sulfoxide.

Standard solution—Transfer 5 mL of the *Standard stock solution* to a 25-mL volumetric flask, and dilute with dimethyl sulfoxide to volume. Transfer 1 mL of the *Standard solution* to a 20-mL headspace vial fitted with a septum and a crimp cap, and seal the vial.

Test solution 1—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of dimethyl sulfoxide, seal the vial, and mix.

Test solution 2—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of *Standard solution,* seal the vial, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame-ionization detector and contains a 0.32-mm × 60-m fused silica column coated with a 1.0-µm film of stationary phase G38. Nitrogen is used as the carrier gas, flowing at a rate of about 25 mL per minute. The column temperature is maintained at 45° for 2 minutes, then increased at a rate of 10° per minute to 75°, then increased at a rate of 5° per minute to 170° and maintained at 170° for 3 minutes. The split injector temperature is maintained at about 200°, and the detector temperature is maintained at about 170°. The transfer loop and transfer line temperature is 170°, and the pressurize time is 0.5 minute. The *Standard solution* vial and the *Test solutions 1* and *2* vials are maintained at about 90°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.55 for methanol, 0.76 for acetonitrile, 1.0 for methylene chloride, 1.2 for *tert*-butyl methyl ether, and 2.3 for dimethylformamide; and the relative standard deviation, determined from peak areas for each peak, for six replicate injections is not more than 10%.

Procedure—Separately inject equal volumes (about 1 mL) of headspace from vials of *Test solution 1* and *Test solution 2* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of methanol, acetonitrile, methylene chloride, *tert*-butyl methyl ether, and dimethylformamide in the Calcitonin Salmon taken by the formula:

$$100(r_{T1})(C)/(r_{T2})(W_{T1}) - (r_{T1})(W_{T2}),$$

in which *C* is the concentration, in mg per mL, of the relevant analyte in the *Standard solution;* W_{T1} and W_{T2} are the weights, in mg, of Calcitonin Salmon taken to prepare *Test solution 1* and *Test solution 2,* respectively; and r_{T1} and r_{T2} are the peak areas of the corresponding analyte obtained

from *Test solution 1* and *Test solution 2,* respectively: not more than 3000 µg of methanol, 400 µg of acetonitrile, 600 µg of methylene chloride, 5000 µg of *tert*-butyl methyl ether, and 900 µg of dimethylformamide per g of Calcitonin Salmon are found.

Acetic acid content—

Internal standard stock solution—Mix 1 mL of dioxane with water to obtain 100 mL of solution.

Standard solution—Transfer approximately 100 mg of glacial acetic acid, accurately weighed, and 10 mL of *Internal standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 10-mL volumetric flask, add 1 mL of *Internal standard stock 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 2-mm × 3-m glass column packed with 10% liquid phase G35, 1% phosphoric acid, on support S1A. Nitrogen is the carrier gas, flowing at a rate of about 30 mL per minute. The column is maintained at 70° for 4 minutes, then increased at a rate of 8° per minute to 120°, then maintained at 120° for 4 minutes. The injection port and detector are maintained isothermally at temperatures of about 200°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between dioxane and acetic acid is not less than 8; and the relative standard deviation for replicate injections is not more than 5.0%.

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 responses of the major peaks. The retention times are about 3 minutes for acetic acid and 1 minute for dioxane. Calculate the percentage of acetic acid in the portion of Calcitonin Salmon taken by the formula:

$$1000(C/W)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of acetic acid in the *Standard solution;* and R_U and R_S are the peak response ratios of acetic acid to dioxane obtained from the *Test solution* and the *Standard solution,* respectively: not less than 4.0% and not more than 15.0% is found.

Bioidentity—

RPMI 1640 with L-glutamine—Prepare a mixture of the ingredients in the quantities shown in sufficient water to obtain 1 L of medium, and sterilize by filtration.

Calcium Nitrate	100.00 mg
Potassium Chloride	400.00 mg
Magnesium Sulfate, Anhydrous	48.84 mg
Potassium Chloride	400 mg
Sodium Chloride	6000 mg
Sodium Phosphate, Dibasic, Anhydrous	800 mg
Sodium Bicarbonate	2000 mg
Glycine	10 mg
L-Arginine	200 mg
L-Asparagine	50 mg
L-Aspartic Acid	20 mg
L-Cystine Dihydrochloride	65 mg
L-Glutamic Acid	20 mg
L-Glutamine	300 mg
L-Histidine	15 mg
L-Hydroxyproline	20 mg
L-Isoleucine	50 mg
L-Leucine	50 mg
L-Lysine Hydrochloride	40 mg

L-Methionine	15 mg
L-Phenylalanine	15 mg
L-Proline	20 mg
L-Serine	30 mg
L-Threonine	20 mg
L-Tryptophan	5 mg
L-Tyrosine Disodium Salt Dihydrate	29 mg
L-Valine	20 mg
Biotin	0.2 mg
Choline Chloride	3 mg
D-Calcium Pantothenate	0.25 mg
Folic Acid	1 mg
i-Inositol	35 mg
Niacinamide	1 mg
Para-Aminobenzoic Acid	1 mg
Pyridoxine Hydrochloride	1 mg
Riboflavin	0.2 mg
Thiamine Hydrochloride	1 mg
Vitamin B_{12}	0.005 mg

Medium A (growth medium)—Using aseptic technique, prepare the following tissue culture medium.

RPMI 1640 with L-glutamine	500 mL
Fetal bovine serum	50 mL
1 M HEPES	5 mL
Penicillin/streptomycin solution (10,000 IU per mL /10 mg per mL)	5 mL
Human insulin	10 IU
Hydrocortisone	0.5 mg

Medium B (stimulation medium)—Dissolve 5 g of albumin bovine serum (BSA), in 500 mL of 2 mM *RPMI 1640 with L -glutamine.*

2% BSA solution—Dissolve 50 mg of albumin bovine serum in 25 mL of water. [NOTE—Use within 1 day.]

Formic acid/BSA solution—Add 25 mL of 0.1 M formic acid and 5 mL of *2% BSA solution* to a 50-mL volumetric flask, and dilute with water to volume. [NOTE—Use within 2 days.]

Trypsin–tetrasodium ethylenediaminetetraacetate (EDTA) solution—Prepare a sterile filtered solution containing 0.25% trypsin and 0.53 mM EDTA.

Dulbecco's phosphate buffered saline—Dissolve 8 g of sodium chloride, 1.15 g of dibasic sodium phosphate, 0.2 g of monobasic potassium phosphate, 0.2 g of potassium chloride, 0.1 g of calcium chloride, and 0.1 g of magnesium chloride in 1 L of water.

Standard stock solution—Dissolve an accurately weighed quantity of USP Calcitonin Salmon RS in *Formic acid/BSA solution* to obtain a solution having a known concentration of about 20 µg per mL.

Positive control solution—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 1 ng per mL.

Negative control solution: Medium B.

Standard solution A—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.1 ng per mL.

Standard solution B—Dilute *Standard solution A* quantitatively with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.033 ng per mL.

Standard solution C—Dilute *Standard solution B* quantitatively (1 : 2) with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.011 ng per mL.

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Standard solution D—Dilute *Standard solution C* quantitatively (1 : 2) with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.0037 ng per mL.

Test stock solution—Dissolve an accurately weighed quantity of Calcitonin Salmon in *Formic acid/BSA solution* to obtain a solution having a concentration of about 20 µg per mL.

Test solution A—Quantitatively dilute the *Test stock solution* with *Medium B* to obtain a solution of Calcitonin Salmon having a concentration of 0.1 ng per mL.

Test solution B—Quantitatively dilute *Test solution A* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.033 ng per mL.

Test solution C—Quantitatively dilute *Test solution B* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.011 ng per mL.

Test solution D—Quantitatively dilute *Test solution C* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.0037 ng per mL.

Cell culture preparation—Prepare cell culture of the human mammary tumor cell line T-47D. Cells are propagated using *Medium A* at 37° and 5% carbon dioxide. The medium is changed every 2 days, and cells are passaged every 5 to 9 days, using *Trypsin–EDTA solution* with a 1 : 4 subculture.

Cell suspension—For the test, use a cell culture that is 5 to 9 days old. Remove the cell culture medium from the flask by aspiration, add 10 mL of *Dulbecco's phosphate buffered saline,* and rock the culture flask to rinse the entire monolayer. Remove the liquid by aspiration, add 2 mL of *Trypsin–EDTA solution,* spread over the entire monolayer, allow to stand for 3 to 5 minutes, and add 10 mL of *Medium A.* Homogenize the cell suspension using a pipet, transfer to a 15-mL polypropylene tube, centrifuge at about 220 × *g* for 5 minutes, pour off the supernatant, and resuspend the cell pellet in 10 mL of *Medium A.* Count the cells, and adjust the cell density through dilution, using *Medium A* to 2.5×10^4 cells per mL.

Procedure—Place 200 µL of the *Cell suspension* into each well of a 96-well culture plate (the *tissue culture plate*), and incubate for 18 to 24 hours at 37° and 5% carbon dioxide. Fill each well of an empty round-bottomed 96-well culture plate (the *prepared plate*) with 150 µL of one of the following solutions: *Positive control solution, Negative control solution, Standard solutions A–D,* and *Test solutions A–D,* so that each solution fills at least five wells on the prepared plate. After incubation, remove the culture medium from the tissue culture plate. Using an 8-channel or 12-channel pipet, rapidly transfer 100 µL of solution from each well of the prepared plate to each well of the tissue culture plate. Incubate for 15 minutes at ambient temperature, remove solution from each well, stop stimulation by immediately adding an appropriate cell-lysis buffer, and quantitate cAMP, produced within the cells, using a validated kit. Perform the test three times, using three different 96-well culture plates. [NOTE—Some kits include a cell-lysis reagent and a sequestering agent for the cell-lysis reagent. The range of the test kit is between 0.05 ng and 10 ng per mL of cAMP.] Potency is determined by a 3-dose, 6-point parallel-line assay, using standard statistical methods. The calculation is carried out using both the lower three concentrations and the upper three concentrations. For the assay to be valid, the requirements for regression and parallelism must be met. If the requirements for validity are met to the same extent in both assessments (the lower and the higher assessments), the final result is determined from the concentration range that shows the higher value when the common slope is divided by the mean square error. The potency levels determined from all three performances of the

test are homogeneous, and the confidence limits for all three determinations are between 64% and 156% of the calculated potency.

Related peptides and other related substances—

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

Solution A, Solution B, Mobile phase, Resolution solution, and *Chromatographic system*—Prepare 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 area percentage of each peak observed in the chromatogram. Disregard any peaks due to the solvent and any peaks whose area is less than 0.1% of the principal peak. No peak other than the principal peak constitutes more than 3.0% of the total area of all peaks. The sum of the area of all peaks apart from the principal peak is not greater than 5.0% of the area of all peaks.

Other requirements—Where the label states that Calcitonin Salmon is sterile, it meets the requirements for *Sterility* under *Calcitonin Salmon Injection.*

Assay—

Solution A—Dissolve 3.62 g of tetramethylammonium hydroxide pentahydrate in 900 mL of water, add 100 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, and degas.

Solution B—Dissolve 1.45 g of tetramethylammonium hydroxide pentahydrate in 400 mL of water, add 600 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, 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⟩).

Standard preparation—Transfer about 10.0 mg of USP Calcitonin Salmon RS, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

Resolution solution—Dissolve the contents of a vial of USP Calcitonin Salmon Related Compound A RS in 0.4 mL of *Solution A,* add 0.1 mL of the *Standard preparation,* and mix.

Assay preparation—Transfer about 10.0 mg of Calcitonin Salmon, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A,* 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 packing L1. The column temperature is maintained at about 65°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–30	72→48	28→52	linear gradient
30–32	48→72	52→28	linear gradient
32–55	72	28	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.15 for calcitonin salmon related compound A and 1.0 for calcitonin salmon; the resolution, *R,* between calcitonin salmon related compound A and calcitonin salmon is not less than 3; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 3%.

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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 of the major peaks. Calculate the percentage of calcitonin salmon in the portion of Calcitonin Salmon taken by the formula:

$$P(W_S / W_U)(r_U / r_S),$$

in which P is the percentage of calcitonin salmon in USP Calcitonin Salmon RS; W_S is the weight, in mg, of USP Calcitonin Salmon RS used to prepare the *Standard preparation;* W_U is the weight, in mg, of Calcitonin Salmon used to prepare the *Assay preparation;* and r_U and r_S are the main peak areas from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Ciprofloxacin, *USP 28* page 476; **Ciprofloxacin Injection,** *USP 28* page 474 and page 42 of *PF* 31(1) [Jan.–Feb. 2005]. Based on the validated data received, it is proposed to replace the test for *Pyrogen* with the test for *Bacterial endotoxins.*

(PA7b: B. Davani) RTS—42022-1

Change to read:

USP Reference standards ⟨11⟩—*USP Ciprofloxacin RS. USP Ciprofloxacin Ethylenediamine Analog RS.*

▲*USP Endotoxin RS.*▲*USP29*
USP Fluoroquinolonic Acid RS.

Change to read:

Other requirements—Where the label states that it is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩ and ~~*Pyrogen*~~

▲*Bacterial endotoxins*▲*USP29*
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*~~

▲*Bacterial endotoxins*▲*USP29*
under *Ciprofloxacin Injection*.

BRIEFING

Ciprofloxacin Injection, *USP 28* page 478 and page 42 of *PF* 31(1) [Jan.–Feb. 2005].—See briefing under *Ciprofloxacin.*

(PA7b: B. Davani) RTS—42023-1

Change to read:

» Ciprofloxacin Injection is a sterile solution of Ciprofloxacin ▲or Ciprofloxacin Hydrochloride▲*USP28* in ~~Sterile Water for Injection~~

▲Water for Injection,▲*USP29*
in 5 percent Dextrose Injection, or in 0.9 percent Sodium Chloride Injection prepared with the aid of Lactic Acid. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

Change to read:

USP Reference standards ⟨11⟩—*USP Ciprofloxacin Ethylenediamine Analog RS. USP Ciprofloxacin Hydrochloride RS.*

▲*USP Endotoxin RS.*▲*USP29*
USP Sodium Lactate RS.

Delete the following:

▲~~Pyrogen—It meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 20 mg of ciprofloxacin per kg.~~▲*USP29*

Add the following:

▲**Bacterial endotoxins** ⟨85⟩—It contains not more than 0.88 USP Endotoxin Unit per mg of ciprofloxacin.▲*USP29*

In-Process Revision

Change to read:

Limit of ciprofloxacin ethylenediamine analog—Proceed as directed in the *Assay* under *Ciprofloxacin*. Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the *Assay preparation* by the formula:

$$100[0.7r_A / (0.7r_A + r_C)],$$

in which 0.7 is the ~~response~~

■correction■1S *(USP28)*
factor for ciprofloxacin ethylenediamine analog; ~~relative to that of ciprofloxacin~~

■■1S *(USP28)*
and r_A and r_C are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than 0.5% of ciprofloxacin ethylenediamine analog.

Change to read:

Dextrose content *(if present)*—Using the undiluted Injection, determine the angular rotation in a suitable polarimeter tube ~~at 25° (see *Optical Rotation* ⟨781⟩). The observed rotation, in degrees, multiplied by 1.0425*A*, in which *A* is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in g, of $C_6H_{12}O_6 \cdot H_2O$ in each 100 mL of Injection taken: between 4.75 and 5.25 g of $C_6H_{12}O_6 \cdot H_2O$ is found.~~

■(see *Optical Rotation* ⟨781⟩). Calculate the percentage (g per 100 mL) of $C_6H_{12}O_6 \cdot H_2O$ in the portion of Injection taken by the formula:

$$(100/52.9)(198.17/180.16)AR,$$

in which 100 is the percentage; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; *A* is 100 mm divided by the length of the polarimeter tube, in mm; and *R* is the observed rotation, in degrees: between 4.75 and 5.25 g of $C_6H_{12}O_6 \cdot H_2O$ is found.■2S *(USP28)*

BRIEFING

Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation, *USP 28* page 486; **Magnesium Carbonate and Citric Acid for Oral Solution,** *USP 28* page 1167; **Magnesium Citrate Oral Solution,** *USP 28* page 1169; **Magnesium Citrate for Oral Solution,** *USP 28* page 1170; **Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution,** *USP 28* page 1582; **Potassium Citrate and Citric Acid Oral Solution,** *USP 28* page 1590; **Potassium Citrate Extended-Release Tablets,** *USP 28* page 1590; **Oral Rehydration Salts,** *USP 28* page 1708 and page 1646 of *PF* 30(5) [Sept.–Oct. 2004]; and **Tricitrates Oral Solution,** *USP 28* page 1971. It is proposed to revise all the assay procedures for citric acid or inorganic citrate and phosphate provided in the respective monographs, and replace the procedures with a single ion chromatography procedure described in the proposed general chapter *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩, which is published elsewhere in this volume of *PF*. In the absence of any significant adverse comment, the revisions are scheduled to appear in *USP 29–NF 24*, but with a delayed implementation date of **January 1, 2009**.

(PA7b: B. Davani; D. Bempong) RTS—42196-5

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Citric Acid RS.*▲*USP29*
USP Endotoxin RS.

(Official January 1, 2009)

Change to read:

Assay for citric acid—

~~*Mobile phase*—Add 2.0 mL of sulfuric acid to 800 mL of water, mix, and dilute with water to 1000 mL. Filter through a membrane filter, heat to 40°, and degas. Maintain the temperature of the *Mobile phase* at 40° throughout the analysis.~~

~~*Standard preparation*—Dissolve a suitable quantity of anhydrous citric acid, accurately weighed, in water to obtain a solution having a known concentration of about 1.2 mg per mL.~~

~~*Resolution solution*—Prepare a solution in water containing about 1 mg of citric acid and about 2 mg of boric acid per mL.~~

~~*Assay preparation*—Transfer an accurately measured volume of Irrigation, equivalent to about 130 mg of citric acid monohydrate, to a 100-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 40°. The flow rate is about 0.6 mL per minute. Chromatograph the *Standard preparation*~~

In-Process Revision

~~and the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.5%, and the resolution, *R,* between the citric acid and boric acid peaks is not less than 4.0.~~

~~*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 mg, of $C_6H_8O_7 \cdot H_2O$ in each mL of the Irrigation taken by the formula:~~

~~$$(210.14/192.12)(100C/V)(r_u/r_s),$$~~

~~in which 210.14 and 192.12 are the molecular weights of citric acid monohydrate and anhydrous citric acid, respectively; *C* is the concentration, in mg per mL, of anhydrous citric acid in the *Standard preparation; V* is the volume, in mL, of Irrigation taken; and r_u and r_s are the peak responses for citric acid obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

▲*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of Irrigation, equivalent to about 130 mg of monohydrate citric acid into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg per mL, of monohydrate citric acid ($C_6H_8O_7 \cdot H_2O$) in the Irrigation taken by the formula:

$$0.001(210.14/189.10)C_S(D/V)(r_U/r_S),$$

in which 210.14 is the molecular weight of monohydrate citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; *V* is the volume, in mL, of Irrigation used in the preparation of the *Assay preparation;* and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1*, respectively.▲*USP29*

(Official January 1, 2009)

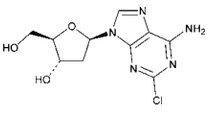
BRIEFING

Cladribine. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on manufacturer's tests and acceptance criteria, is being proposed. The reverse phase HPLC procedures in the test for *Related compounds* and in the *Assay* were validated using a Shimadzu Premier brand of L1 column; cladribine elutes at approximately 8.1 minutes.

(PA6: L. Evans; PSD: C. Okeke; NL: C. Barnstein) RTS—41567-1; 41567-2; 41911-1

Add the following:

▲Cladribine



$C_{10}H_{12}ClN_5O_3$ 285.69

Adenosine, 2-chloro-2′-deoxy-.

2-Chloro-2′-deoxyadenosine [*4291-63-8*].

» Cladribine contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}ClN_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and protect from light. Store between 2° and 8°.

USP Reference standards ⟨11⟩—*USP Cladribine RS. USP Cladribine Related Compound A RS.*

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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 –17° and –21°.

Test solution: 10 mg per mL, in dimethylformamide.

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Buffer, Diluent, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; and the tailing factor is not more than 2.0.

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 Cladribine taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the individual peak response of each individual impurity, and r_s is the sum of the responses of all the peaks. Refer to *Table 1* for the impurity limits.

Table 1

Name	Relative Retention Time	Limit (%)
2,6-Diaminopurine-2′-deoxyriboside	about 0.41	0.2
2′-Deoxyadenosine	about 0.47	0.2
2-Chloroadenine	about 0.60	0.2
2-Methoxy-2′-deoxyadenosine (cladribine related compound A)	about 0.91	0.2
Any other individual impurity	—	0.1
Total impurities	—	1.0

Limit of residual solvents—

Standard solution—Transfer 15 µL of methanol and 24 µL of alcohol to a 100-mL volumetric flask containing 80 mL of water, dilute with water to volume, and mix. Transfer 3 mL of the solution to a 20-mL headspace vial. The concentrations of methanol and alcohol in the *Standard solution* are 119 µg per mL and 198 µg per mL, respectively.

Test solution—In a 20-mL headspace vial, dissolve 200 mg of Cladribine, accurately weighed, in 5 mL of water.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame-ionization detector and contains a 0.53-mm × 30-m column coated with a 5-µm film of liquid phase G16. The carrier gas is nitrogen, flowing at a rate of 4 mL

per minute. The split ratio is 5 : 1. Vials containing the *Standard solution* and the *Test solution* are equilibrated for 10 minutes at 80° in the headspace sampler. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 80° for 6 minutes, then increased at a rate of 25° per minute to 240° and held at 240° for 20 minutes. The injection port temperature is maintained at 250°, and the detector temperature is maintained at 250°. Chromatograph the *Standard soluation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between alcohol and methanol is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10.0% for each of the two solvents.

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 responses for the major peaks. Calculate the concentration, in ppm, of each residual solvent in the portion of Cladribine by the formula:

$$5000(C/W)(r_U / r_S),$$

in which C is the concentration, in µg per mL, of the respective individual solvent in the *Standard solution; W* is the quantity, in mg, of Cladribine 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 5000 ppm of alcohol is found, and not more than 450 ppm of methanol is found.

Assay—

Buffer—Dissolve 9.96 g of triethylamine phosphate, accurately weighed, in 500 mL of water, and add another 500 mL of water. Adjust with potassium hydroxide to a pH of 6.1.

Diluent—Prepare a mixture of water and methanol (90 : 10).

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and methanol (78 : 22). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Cladribine RS and USP Cladribine Related Compound A RS in *Diluent* to obtain known concentrations of about 2.0 mg per mL each.

Standard preparation—Dissolve an accurately weighed quantity of USP Cladribine RS in *Diluent* to obtain a concentration of 0.5 mg per mL.

Assay preparation—Transfer about 25 mg of Cladribine, accurately weighed, to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; the tailing factor for the cladribine peak in the *System suitability solution* is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* 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 $C_{10}H_{12}ClN_5O_3$ in the portion of Cladribine taken by the formula:

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

in which *C* is the concentration, in mg per mL, of USP Cladribine 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.▲*USP29*

BRIEFING

Clotrimazole Lozenges, *USP 28* page 521. It is proposed to replace the *Disintegration* test with a *Dissolution* test. The liquid chromatographic procedure was developed using a NovaPak C18 brand of column that contains L1 packing. The retention time of clotrimazole is about 6 minutes.

(BPC: M. Marques) RTS—41769-1

Delete the following:

▲~~**Disintegration** ⟨701⟩: 30 minutes, but complete disintegration does not occur before 5 minutes.~~▲*USP29*

Add the following:

▲**Dissolution** ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{22}H_{17}ClN_2$ dissolved by employing the following method.

25 mM Phosphate buffer—Dissolve 4.4 g of dibasic potassium phosphate in 1000 mL of water.

100 mM Phosphate buffer—Dissolve 17.4 g of dibasic potassium phosphate in 1000 mL of water.

Diluent—Prepare a filtered and degassed mixture of methanol and *100 mM Phosphate buffer* (60 : 40).

Mobile phase—Prepare a filtered and degassed mixture of methanol and *25 mM Phosphate buffer* (4 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Clotrimazole RS, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a concentration of about 0.02 mg per mL.

Working standard solution—Transfer 5.0 mL of the *Standard solution* to a 25-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polyvinylidene difluoride filter, discarding the first 10 mL of the filtrate. Transfer 5.0 mL of the filtrate 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 215-nm detector and a 3.9-mm × 7.5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working 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 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in percentage, of $C_{22}H_{17}ClN_2$ released by the formula:

$$\frac{r_U \times C_S \times 500 \times D \times 100}{r_s \times LC},$$

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in which r_U and r_S are the peak responses for the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution; D* is the dilution factor of the *Working standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{22}H_{17}ClN_2$ is dissolved in 45 minutes.▲*USP29*

BRIEFING

Dibucaine, *USP 28* page 622; **Dibucaine Cream,** *USP 28* page 623; **Dibucaine Ointment,** *USP 28* page 623; **Dibucaine Hydrochloride,** *USP 28* page 623 and page 1458 of *PF* 29(5) [Sept.–Oct. 2003]; and **Dibucaine Hydrochloride Injection,** *USP 28* page 624. It is proposed to revise the *Identification* test by replacing the UV absorption spectra comparison with HPLC retention time agreement of the major peak in the *Assay preparation* and the *Standard preparation*. The proposed revision is consistent with current pharmaceutical industry practice.

(PA1: K. Russo) RTS—41743-8

Change to read:

Identification—

A: The IR absorption spectrum of a mineral oil dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar dispersion of the residue prepared by dissolving 30 mg of USP Dibucaine Hydrochloride RS in 5 mL of 0.5 N sodium hydroxide, extracting the resulting solution with 5 mL of ether, evaporating the ether, and drying the residue over phosphorus pentoxide.

~~**B:** *Ultraviolet Absorption* ⟨197U⟩—~~
~~*Solution:* 10 µg per mL.~~
~~*Medium:* 1 N hydrochloric acid.~~
~~Molar absorptivities of the specimen and the USP Dibucaine Hydrochloride RS at 247 nm, calculated on the dried basis, do not differ by more than 3.0%.~~

▲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.*▲*USP29*

BRIEFING

Dibucaine Cream, *USP 28* page 623—See briefing under *Dibucaine*. The *Standard preparation* in the *Assay* is revised to indicate the target concentration rather than a specific weight of Reference Standard material.

(PA1: K. Russo) RTS—41743-3

Change to read:

Identification—~~The UV absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the solution of USP Dibucaine Hydrochloride RS prepared as directed in the *Assay.*~~

▲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.*▲*USP29*

Change to read:

Assay—

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

Standard preparation—~~Transfer about 25 mg of USP Dibucaine Hydrochloride RS, accurately weighed, to a 100-mL volumetric flask, add 20.0 mL of 0.1 N hydrochloric acid, and swirl to dissolve. Dilute with methanol to volume, and mix. Pass through a suitable filter of 0.5 µm or finer porosity.~~

▲Dissolve an accurately weighed quantity of USP Dibucaine Hydrochloride RS in an amount of 0.1 N hydrochloric acid equivalent to 20% of the flask's volume, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL.▲*USP29*

Assay preparation—Weigh accurately a portion of Cream, equivalent to about 22 mg of dibucaine, transfer to a separator containing 25 mL of ether, and mix to dissolve. Extract successively with two 9-mL portions of 0.1 N hydrochloric acid, combining the extracts in a 100-mL volumetric flask. Extract the ether phase in the separator with 2 mL of water, collecting the aqueous extract in the 100-mL volumetric flask. Dilute with methanol to volume, and mix. Pass through a suitable filter of 0.5-µm or finer porosity.

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 re-

sponses for the major peaks. Calculate the quantity, in mg, of dibucaine ($C_{20}H_{29}N_3O_2$) in the portion of Cream taken by the formula:

$$(343.46/379.93)(100C)(r_U / r_S),$$

in which 343.46 and 379.93 are the molecular weights of dibucaine and dibucaine hydrochloride, respectively; C is the concentration, in mg per mL, of USP Dibucaine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the area responses of the dibucaine peaks obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Dibucaine Ointment, *USP 28* page 623—See briefing under *Dibucaine*.

(PA1: K. Russo) RTS—41743-4

Change to read:

Identification— ~~The UV absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the solution of USP Dibucaine Hydrochloride RS prepared as directed in the *Assay*.~~

▲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.*▲*USP29*

BRIEFING

Dibucaine Hydrochloride, *USP 28* page 623 and page 1458 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Dibucaine*.

(PA1: K. Russo) RTS—41743-9

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 (*USP28*)

Change to read:

USP Reference standards ⟨11⟩—*USP Dibucaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP28*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: ~~*Ultraviolet Absorption* ⟨197U⟩—~~

~~*Solution:* 10 µg per mL.~~

~~*Medium:* 1 N hydrochloric acid.~~

~~Absorptivities at 247 nm, calculated on the dried basis, do not differ by more than 3.0%.~~

▲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.*▲*USP29*

C: A solution of it responds to the tests for *Chloride* ⟨191⟩ when tested as specified for alkaloidal hydrochlorides.

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 (*USP28*)

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BRIEFING

Dibucaine Hydrochloride Injection, *USP 28* page 624—See briefing under *Dibucaine*.

(PA1: K. Russo) RTS—41743-7

Change to read:

Identification—

A: ~~The UV absorption spectrum of the *Assay preparation,* prepared as directed in the *Assay,* exhibits maxima and minima at the same wavelengths as that of the *Standard preparation,* prepared as directed in the *Assay,* concomitantly measured.~~

▲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.*▲*USP29*

B: Place a volume of Injection, equivalent to about 30 mg of dibucaine hydrochloride, in a suitable evaporating dish, and concentrate on a steam bath to a volume of about 10 mL. Transfer the solution to a separator, render distinctly alkaline with 1 N sodium hydroxide, and extract with four 20-mL portions of ether. Wash the combined ether extracts with 5 mL of water, discarding the washing. Evaporate the ether extracts with the aid of a current of air to dryness, and dry the residue over phosphorus pentoxide for 3 hours: the dibucaine so obtained melts between 62° and 65°.

BRIEFING

Dorzolamide Hydrochloride, *USP 28* page 691. It is proposed to revise the test for *Limit of dorzolamide hydrochloride related compound A* to delete the relative standard deviation (RSD) requirement and to revise the *Assay* to modify the acetonitrile content in the *Mobile phase*.

(PA6: L. Evans) RTS—41323-1; 41335-1; 41335-2; 41335-3

Change to read:

Limit of dorzolamide hydrochloride related compound A—

Mobile phase—Prepare a filtered and degassed mixture of *tert*-butyl methyl ether, chromatographic *n*-heptane, acetonitrile, and water (63 : 35 : 2 : 0.2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 18 mg of USP Dorzolamide Hydrochloride RS and 2 mg of USP Dorzolamide Hydrochloride Related Compound A RS, each accurately weighed, to a 15-mL centrifuge tube, dissolve in 4 mL of 0.5 N ammonium hydroxide, add 4 mL of ethyl acetate, and mix. Separate the ethyl acetate layer, and transfer to a 15-mL centrifuge tube. Add 4 mL of ethyl acetate to the aqueous layer, mix, separate the ethyl acetate layer, and combine it with the first extract. Evaporate the combined organic layers to dryness on a water bath maintained at 50° under a stream of nitrogen. Dissolve the residue in 3 mL of acetonitrile, add 3 drops of *(S)*-(–)-α-methylbenzyl isocyanate ▲[NOTE—Discard the reagent if it is colored.],▲*USP28* and allow to react for 5 minutes on a water bath maintained at 50°. ▲▲*USP28* Evaporate the mixture to dryness on a water bath maintained at 50° under a stream of nitrogen. Dissolve the residue in 10 mL of a mixture of *tert*-butyl methyl ether, glacial acetic acid, and acetonitrile (87 : 10 : 3).

Test solution—Transfer about 20 mg of Dorzolamide Hydrochloride, accurately weighed, to a 15-mL centrifuge tube, and proceed as directed for *System suitability solution* beginning with "dissolve in 4 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 packing L3. The flow rate is about 2 mL per minute. Chromatograph the *System suitability solution,* and record the peak ▲areas▲*USP28* as directed for *Procedure:* the relative retention times are about 1.0 for dorzolamide and 1.5 for dorzolamide hydrochloride related compound A; the resolution, *R,* between dorzolamide and dorzolamide hydrochloride related compound A is not less than 4.0; the column efficiency ▲for the dorzolamide hydrochloride peak▲*USP28* is not less than ▲4000▲*USP28* theoretical plates; and the tailing factor is not more than 1.4. ~~; and the relative standard deviation for replicate injections determined from the dorzolamide peak is not more than 1.0%.~~

▲▲*USP29*

Procedure—Separately inject equal volumes (about 10 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ▲areas for▲*USP28* the major peaks. Calculate the percentage of dorzolamide hydrochloride related compound A in the portion of Dorzolamide Hydrochloride taken by the formula:

$$▲100r_1 / (r_1 + r_S),$$

in which r_1 is the peak area of dorzolamide hydrochloride related compound A obtained from the *Test solution;* and r_S is the peak area of dorzolamide hydrochloride obtained from the *Test solution:* not more than 0.5% is found.▲*USP28*

Change to read:

Assay—

▲*Phosphate buffer*▲*USP28*—Dissolve 3.7 g of

▲monobasic▲*USP29*
potassium phosphate in ▲1000 mL▲*USP28* of water.

▲*Solution A*—Prepare a filtered and degassed mixture of ~~monobasic *Phosphate buffer* and acetonitrile (94 : 6).~~

▲*Phosphate buffer* and acetonitrile (94 : 6.5).▲*USP29* ▲*USP28*

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⟩).

Standard preparation—Dissolve suitable quantities of USP Dorzolamide Hydrochloride RS in *Solution A* to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer about 60 mg of Dorzolamide Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Solution A* 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. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–15	100	0	isocratic
15–30	100→50	0→50	linear gradient
30–37	50→100	50→0	linear gradient
37–44	100	0	isocratic

Chromatograph the *Standard preparation,* and record the peak ▲areas▲*USP28* as directed for *Procedure:* the column efficiency is not less than 6500 theoretical plates; the tailing factor is not less than 0.6 and not more than 1.2; and the relative standard deviation for replicate injections 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▲*USP28* for the major peaks. Calculate the quantity, in mg, of $C_{10}H_{16}N_2O_4S_3 \cdot HCl$ in the portion of Dorzolamide Hydrochloride taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Dorzolamide Hydrochloride 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.

BRIEFING

Ethinyl Estradiol Tablets, *USP 28* page 789 and page 1112 of *PF* 28(4) [July–Aug. 2002]. It is proposed to increase the limit of any unknown impurity to the approved value of 0.3% in the test for *Related compounds.* In addition, minor editorial changes have been made.

(PA1: C. Anthony) RTS—42252-1

In-Process Revision

Delete the following:

■~~**Disintegration** ⟨701⟩: 30 minutes.~~■2S (*USP28*)

Add the following:

■**Dissolution** ⟨711⟩—[To come.]■2S (*USP28*)

Change to read:

Related compounds—

Solution A: acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50 : 50).

Solution B: 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 for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and water (50 : 50).

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—Quantitatively dilute portions of *Standard stock solution* with *Diluent* to obtain a solution containing about 0.12 µg per mL of USP Ethinyl Estradiol RS.

Test solution 1—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 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 210-nm 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 contains packing L11. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution	Flow rate (mL per min.)
0–20	100	0	equilibration/ isocratic	2
20–25	100→0	0→100	linear gradient	2.5
25–30	0	100	isocratic	3
30–32	0→100	100→0	linear gradient	2
32–35	100	0	re-equilibration	2

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0 for ethinyl estradiol; and the relative standard deviation for replicate injections is not more than 2.0%.

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 the relative retention time of 1.16; 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 the relative retention time of 1.2; 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 any other impurity taken by the formula:

$$100(r_U/r_S),$$

in which r_U 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. Not more than 0.5% of 17β-ethinyl estradiol is found; not more than 0.5% of estrone is found; not more than ~~0.1%~~

▲0.3%▲*USP29*
of any unknown impurity is found; and not more than 2.0% of total impurities is found.

BRIEFING

Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is proposed. The liquid chromatographic system used in the *Related compounds* and *Assay* procedures was validated using an Alltech Adsorbosphere XL SCX brand of L6 column connected in series to a Zorbax SB-phenyl brand of L11 column. Typical retention times are about 4.2 minutes for pseudoephedrine, 5.0 minutes for ephedrone, 7.5 minutes for fexofenadine, 9.2 minutes for fexofenadine related compound A, and 23.6 minutes for fexofenadine related compound B. The *Dissolution* test was validated using a Partisil 10 SCX brand of L6 column. Typical retention times are about 4.3 minutes for fexofenadine and about 6.4 minutes for pseudoephedrine.

(PA1: K. Russo; BPC: M. Marques; PSD: C. Okeke; NL: L. Paul) RTS—40154-1; 40154-2; 40154-3; 40512-3; 41192-2

Add the following:

▲Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

» Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Fexofenadine Related Compound B RS. USP Pseudoephedrine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

FEXOFENADINE HYDROCHLORIDE—

Test specimen—Grind the fexofenadine hydrochloride layer of 1 Tablet, and transfer it into a 30-mL capped centrifuge tube. Add 20 mL of 1 N sodium hydroxide, mix in a vortex mixer for 1 to 2 minutes, then centrifuge for 3 to 5 minutes at approximately 2500 rpm or greater. Decant the solution, and pass through a 25-mm glass syringe filter. Add 10 mL of 10% hydrochloric acid, and heat this solution, with stirring, to near boiling. Cool, and centrifuge for 3 to 5 minutes. Decant and discard the liquid, wash the precipitate with 10 mL of water, and centrifuge for 1 to 2 minutes. Decant and discard the water, and dry the precipitate in an oven for 1 hour at 105°.

Standard specimen—Transfer a quantity, in mg, of USP Fexofenadine Hydrochloride RS, equivalent to the labeled amount of fexofenadine hydrochloride, to a 30-mL capped centrifuge tube, and proceed as directed beginning with "Add 20 mL of 1 N sodium hydroxide".

PSEUDOEPHEDRINE HYDROCHLORIDE—

Test specimen—Grind the pseudoephedrine hydrochloride layer of 1 Tablet, and transfer it into a capped 30-mL centrifuge tube. Add 20 mL of 0.1 N hydrochloric acid, mix on a vortex mixer for 1 to 2 minutes, and centrifuge for 3 to 5 minutes at approximately 2500 rpm or greater. Decant the solution, and pass through a 0.45-µm nylon filter; discard the residue. Add 10 mL of 1 N sodium hydroxide, and pour it into a separatory funnel containing 15 mL of methylene chloride. Carefully rotate and shake the funnel using care not to form an emulsion. Allow the layers to separate for

about 10 minutes. Decant the methylene chloride (lower) layer into a 50-mL beaker, and filter through a glass funnel loaded with a glass wool plug and 1 to 2 g of sodium sulfate. Evaporate to dryness. [NOTE—Do not exceed 75° if a hot plate is used to aid evaporation.]

Standard specimen—Transfer a quantity, in mg, of USP Pseudoephedrine Hydrochloride RS equivalent to the labeled amount of pseudoephedrine hydrochloride to a 30-mL capped centrifuge tube, and proceed as directed beginning with "Add 20 mL of 0.1 N hydrochloric acid".

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: 0.001 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Times: fexofenadine hydrochloride: 15 and 45 minutes; pseudoephedrine hydrochloride: 45 minutes; 3, 5, and 12 hours.

Procedure—Determine the percentages of the labeled amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved by using the following method.

Buffer solution—Dissolve 14.0 g of monobasic sodium phosphate monohydrate in 2 L of water. Adjust with 85% phosphoric acid to a pH of 2.00 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (55 : 45). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard solution—[NOTE—A small amount of methanol, not to exceed 0.5% of the total volume, can be used to dissolve the fexofenadine hydrochloride.] Dissolve an accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, to obtain a solution containing known concentrations similar to that expected in the solution under test.

Test solution—Use portions of the solution under test passed through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column containing packing L6. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R*, between fexofenadine and pseudoephedrine is not less than 3.0; the tailing factor is not more than 1.5 for fexofenadine and for pseudoephedrine; 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, and record the peak responses for fexofenadine and pseudoephedrine. Calculate the amounts of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved.

Tolerances—For fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$), not less than 65% (*Q*) of the labeled amount is dissolved in 15 minutes and not less than 80% (*Q*) of the labeled amount is dissolved in 45 minutes; the percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times speci-

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fied conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩ (*Acceptance Table 2* under *Dissolution* ⟨711⟩, Official April 1, 2006).

Time	Amount dissolved (average)
45 minutes	not more than 36%
3 hours	between 45% and 69%
5 hours	between 61% and 80%
12 hours	not less than 80%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Water, *Method I* ⟨921⟩**—**Weigh and finely powder not fewer than 5 Tablets, and transfer an accurately weighed quantity of the powder, about 250 mg, to a jacketed titration vessel containing titration medium heated to 50°: between 1.0% and 4.0%.

Related compounds—

Buffer solution, Mobile phase, System suitability preparation, and *Chromatographic system*—Proceed as directed under *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Reference solution—Use the *Assay preparation.*

Test solution—Use the *Stock assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability preparation* as directed for *Procedure:* the relative retention times are about 1.2 for ephedrone and 1.0 for pseudoephedrine; the resolution, *R*, between pseudoephedrine and ephedrone is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for fexofenadine related compound B, and 1.0 for fexofenadine; the resolution, *R*, between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak and not more than 3.0% based on the individual peaks for fexofenadine related compound A and fexofenadine related compound B.

Procedure—Inject volumes (about 20 µL) of the *Test solution* and of the *Reference solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of fexofenadine related compound A and fexofenadine related compound B in the portion of Tablets taken by the formula:

$$(100/L)(C_S/C_T)(r_i/r_S),$$

in which L is the label claim for fexofenadine hydrochloride; C_S is the concentration, in mg per mL, of either USP Fexofenadine Related Compound A RS or USP Fexofenadine Related Compound B RS in the *Standard solution;* C_T is the nominal concentration, in mg per mL, of fexofenadine in the *Test solution;* r_i is the individual peak area of either fexofenadine related compound A or fexofenadine related compound B obtained from the *Test solution;* and r_S is the peak area of fexofenadine related compound A obtained from the *Standard solution*. Calculate the percentage of ephedrone in the portion of Tablets taken by the formula:

$$(100/LF)(C_S C_T)\ (r_i/r_S),$$

in which L is the label claim for pseudoephedrine hydrochloride; F is the relative response factor for ephedrone (F is 0.394); C_S is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the *Standard*

solution; C_T is the nominal concentration, in mg per mL, of pseudoephedrine in the *Test solution;* r_i is the peak height for ephedrone obtained from the *Test solution;* and r_S is the peak height for pseudoephedrine obtained from the *Standard solution*. Calculate the percentage of any other impurities in the portion of Tablets taken by the formula:

$$100r_i / (25r_S + r_T),$$

in which r_i is the individual peak area response for an individual unknown impurity in the *Test solution;* 25 is the difference in concentration between the *Test solution* and the *Reference solution;* r_S is the peak area response for fexofenadine in the *Reference solution;* and r_T is the sum of the peak area responses of all unknown impurities in the *Test solution*. Disregard any peak below 0.05%.

Compound	Relative Retention Time	Acceptance Criteria
Pseudoephedrine	1.0	—
Ephedrone	1.2[a]	not more than 0.2%
Fexofenadine	1.0	—
Fexofenadine related compound A	1.2[b]	not more than 0.3%
Fexofenadine related compound B	3.1[b]	not more than 0.2%
Any individual other impurity	—	not more than 0.1%
Total other impurities	—	not more than 0.2%
Total impurities	—	not more than 0.5%

[a] Relative to pseudoephedrine
[b] Relative to fexofenadine

Assay—

Buffer solution—Dissolve 6.8 g of sodium acetate and 16.22 g of sodium 1-octanesulfonate in water, and dilute with water to 1 L. Adjust with glacial acetic acid to a pH of 4.6.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Transfer an accurately weighed quantity, about 40 mg, of USP Pseudoephedrine Hydrochloride RS to a 50-mL volumetric flask. Add 5 mL of *tert*-butylhydroperoxide solution, and sonicate. Cover the flask opening with aluminum foil, and place the flask in an oven at about 90° for 60 minutes. Remove from the oven, and allow to cool. Add 35 mL of *Mobile phase,* and cool to room temperature. Dilute with *Mobile phase* to volume, and mix. The degradation of pseudoephedrine hydrochloride by this process produces the related compound ephedrone.

Related compounds preparation—Dissolve accurately weighed quantities of USP Fexofenadine Related Compound A RS and USP Fexofenadine Related Compound B RS in a volume of methanol, and dilute qualitatively, and stepwise if necessary, with *Buffer solution* to maintain a ratio of methanol and *Buffer solution* (60 : 40). Dilute quantitatively, and stepwise if necessary, with methanol and *Buffer solution* (60 : 40) to obtain a solution having known concentrations of 0.2 mg per mL for each component. Dilute 10.0 mL of this solution with *Mobile phase* to 100 mL to obtain the final solution, having known concentrations of 0.02 mg per mL for each component.

Standard stock preparation—Dissolve accurately weighed quantities of USP Fexofenadine Hydrochloride RS and USP Pseudoephedrine Hydrochloride RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary,

with *Mobile phase* to obtain a solution having known concentrations of about 0.4 mg per mL and 0.8 mg per mL of fexofenadine and pseudoephedrine, respectively.

Standard preparation—Dilute 6.0 mL of the *Standard stock preparation* and 15.0 mL of the *Related compounds preparation* with *Mobile phase* to 50 mL to obtain a solution having known concentrations of about 0.048 mg of fexofenadine hydrochloride per mL, 0.096 mg of pseudoephedrine hydrochloride per mL, 0.006 mg of fexofenadine related compound A per mL, and 0.006 mg of fexofenadine hydrochloride related compound B per mL.

Assay stock preparation—Transfer not fewer than 10 whole Tablets to a 500-mL volumetric flask. Add 300 mL of methanol, and shake by mechanical means at high speed for 60 minutes. Sonicate the flask for 60 minutes at 40°. Add 150 mL of *Buffer solution,* and sonicate for 60 minutes at 40°. Vent the flask, and vigorously shake the flask by hand at 15-minute intervals during the mechanical shaking and sonication steps. Cool to room temperature, and dilute with *Buffer solution* to volume to obtain a solution containing approximately 1.2 mg of fexofenadine per mL and 2.4 mg of pseudoephedrine 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—Dilute 4.0 mL of the *Assay stock preparation* filtrate with *Mobile phase* to 100 mL. The final concentrations of fexofenadine and pseudoephedrine are 0.048 and 0.096 mg per mL, respectively.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and 4.6-mm × 5-cm column that contains 5-µm packing L6 connected in series to a 4.6-mm × 25-cm column that contains 5-µm packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation* as directed for *Procedure:* the relative retention times are about 1.2 for ephedrone and 1.0 for pseudoephedrine; the resolution, *R*, between pseudoephedrine and ephedrone is not less than 1.7; and the relative standard deviation for replicate injections is not more than 1.0% based on the pseudoephedrine peak. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for fexofenadine related compound A, 3.1 for fexofenadine related compound B, and 1.0 for fexofenadine; the resolution, *R*, between fexofenadine and fexofenadine related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0% based on the fexofenadine peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine and pseudoephedrine peaks. Calculate the percentage of the label claim of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken by the formula:

$$(100/L)(C_S/C_T)(r_U/r_S),$$

in which L is the label claim of either fexofenadine hydrochloride or pseudoephedrine hydrochloride; C_S is the concentration, in mg per mL, of either USP Fexofenadine Hydrochloride RS or USP Pseudoephedrine Hydrochloride RS in the *Standard preparation;* C_T is the nominal concentration, in mg per mL, of either fexofenadine or pseudoephedrine in the *Assay preparation;* and r_U and r_S are the peak responses obtained for either fexofenadine or pseudoephedrine from the *Assay preparation* and the *Standard preparation*, respectively.▲*USP29*

In-Process Revision

BRIEFING

Fluconazole, *USP 28* page 828. It is proposed to add a *Labeling* section to indicate that it is necessary to state with which test for *Related compounds* the article complies only if a test other than *Test 1* is used. Additionally, it is proposed to revise the acceptance criteria for the impurity levels as well as for the Definition to reflect different manufacturing processes for the drug substance.

(PA7b: B. Davani) RTS—42229-1

Change to read:

» Fluconazole contains not less than ~~98.5~~

▲98.0▲*USP29*
percent and not more than ~~101.5~~

▲102.0▲*USP29*
percent of $C_{13}H_{12}F_2N_6O$, calculated on the dried basis.

Add the following:

▲**Labeling**—If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test(s) the article complies.▲*USP29*

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Desacetyl Diltiazem Hydrochloride RS.*▲*USP29*
USP Fluconazole RS. USP Fluconazole Related Compound A RS. USP Fluconazole Related Compound B RS. USP Fluconazole Related Compound C RS.

Change to read:

Related compounds—

▲[NOTE—On the basis of information regarding the manufacturing process, perform either *Test 1* or *Test 2* and *Test 3*.]

TEST 1—▲*USP29*

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

System suitability solution—Use the *Standard solution*.

Standard solution—Transfer accurately weighed quantities of USP Fluconazole RS, USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, and USP Fluconazole Related Compound C RS to a suitable volumetric flask, dissolve in acetonitrile, dilute quantitatively, and stepwise if necessary, with *Mobile phase* to volume, and mix to obtain a solution having known concentrations of 10 µg of each per mL.

Test solution—Transfer about 30 mg of Fluconazole, 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 260-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L1. The flow rate is about 0.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* typical retention times are about 4.9 minutes for fluconazole related compound A, 8.0 minutes for fluconazole related compound B, 8.5 minutes for fluconazole related compound C, and 9.9 minutes for fluconazole; the resolution, *R,* between fluconazole related compound B and fluconazole related compound C is not less than 1.5; and the relative standard deviation of each peak 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, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fluconazole related compound A, fuconazole related compound B, fluconazole related compound C, and any other impurities in the portion of Fluconazole taken by the formula:

$$1000(C/W)(r_U/r_S),$$

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

▲not more than 1.0% of any impurity with a relative retention time (RRT) of about 0.6 is found; not more than 0.2% of any impurity with an RRT of 0.5 or an RRT of about 0.9 is found; not more than 0.1% of any other individual impurity is found; not more than 0.2% of total other impurities is found; and not more than 1.2% of total impurities is found.

TEST 2—

Acetate buffer—Prepare a 0.04 M anhydrous sodium acetate solution, adjust with 1 N acetic acid to a pH of 5.0, and mix.

Solution A: filtered and degassed *Acetate buffer.*

Solution B: acetonitrile.

Solution C: methanol.

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

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Diluent—Prepare a mixture of *Acetate buffer* and methanol (84 : 16).

Standard solution—Dissolve an accurately weighed quantity of USP Fluconazole RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.01 mg per mL.

System suitability solution—Dissolve suitable quantities of USP Fluconazole RS and USP Desacetyl Diltiazem Hydrochloride RS in *Diluent.* Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution containing about 0.02 mg per mL and 0.006 mg per mL, respectively.

Test solution—Transfer about 200 mg of Fluconazole, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 261-nm detector and a 4.0-mm × 10-cm column that contains packing L1. The flow rate is 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–10	80	5	15	isocratic
10–20	80→30	5→55	15	linear gradient (*A* and *B*)
20–23	30	55	15	isocratic
23–25	30→80	55→5	15	reset composition
25–30	80	5	15	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.0 for fluconazole and about 1.2 for desacetyl hydrochloride; the resolution, *R,* between fluconazole and desacetyl diltiazem hydrochloride is not less than 10.0; the column efficiency for fluconazole is not less than 30,000 theoretical plates; and the tailing factor, *T,* is not more than 1.4. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is less 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, and measure the peak responses. Calculate the percentage of each impurity in the portion of Fluconazole taken by the formula:

$$10{,}000(r_i / r_S)(C/W)(1/F),$$

in which r_i is the peak response of each impurity obtained from the *Test solution;* r_S is the peak response of fluconazole obtained from the *Standard solution; C* is the concentration, in mg per mL, of USP Fluconazole RS in the *Standard solution; W* is the weight, in mg, of Fluconazole taken to prepare the *Test solution;* and *F* is the relative response factor as determined from the following table.

Relative Response Factor *(F)*	Relative Retention Time (RRT)
0.72	0.17–0.37
0.85	1.20–1.32
1.21	0.48–0.60
0.96	1.14–1.18
0.97	0.67–0.79
1.0	all other peaks

Not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

TEST 3—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve an accurately weighed quantity of Fluconazole in methanol to obtain a solution containing approximately 50 mg per mL.

Standard solutions—Dissolve an accurately weighed quantity of USP Fluconazole RS in methanol to obtain *Standard solution A* having a known concentration of about 1 mg per mL (2.0%). Quantitatively dilute portions of this solution with methanol to obtain *Standard solution B* and *Standard solution C* having known concentrations of about 0.1 mg per mL (0.2%) and 0.05 mg per mL (0.1%), respectively.

Developing solvent system—Prepare a mixture of chloroform, methanol, and ammonium hydroxide (80 : 20 : 1).

Application volume: 10 µL.

Spray reagent A—Dissolve about 170 mg of silver nitrate in 100 mL of water.

Spray reagent B (Potassium iodoplatinate solution)—Dissolve about 375 mg of chloroplatinic acid in 5 mL of 1 N hydrochloric acid. Dissolve about 5 g of potassium iodide in 50 mL of water, and store in a light-resistant container. Prepare a mixture of water, the potassium iodide solution, and the chloroplatinic acid solution (20 : 9 : 1).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Spray the dry plate with *Spray reagent A,* and expose the plate to 365-nm UV light for 10 to 20 minutes. Dry the plate for 20 minutes between 80° and 90°, then spray the plate with *Spray reagent B*. Allow the plate to dry. Examine the plate 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:* no spot from the chromatogram of the *Test solution* with an R_F value of between 0.10 to 0.25 and 0.27 to 0.41 is larger or more intense than that obtained from *Standard solution B* (0.2%).▲*USP29*

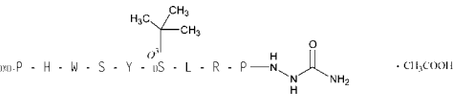
BRIEFING

Goserelin Acetate. 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 *Limit of acetic acid* are based on analyses performed with the Aminex HPX-87H brand of L17 column. The typical retention time for acetic acid is about 11.5 minutes. The liquid chromatographic procedures in the test for *Related substances* and in the *Assay* are based on analyses performed with the X-Terra MS C18 brand of L1 column. The goserelin peak elutes at approximately 45 minutes.

(BNT: L. Callahan) RTS—41757-1

Add the following:

▲Goserelin Acetate



$C_{59}H_{84}N_{18}O_{14} \cdot xC_2H_4O_2$

Luteinizing hormone-releasing factor (pig), 6-[*O*-(1,1-dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide, acetate (salt) [*145781-92-6*].

1-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)-semicarbazide (Goserelin) 1269.41 [*65807-02-5*].

» Goserelin Acetate is a synthetic nonapeptide analog of the hypothalmic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate salt. It contains not less than 94.5 percent and not more than 103.0 percent of goserelin ($C_{59}H_{84}N_{18}O_{14}$), calculated on the anhydrous and acetic acid-free basis.

In-Process Revision

Packaging and storage—Preserve in a tight, light-resistant container, and store in a refrigerator.

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Goserelin Acetate RS. USP Goserelin Related Compound A RS. USP Goserelin Validation Mixture RS.*

Identification—

A: *Nuclear Magnetic Resonance* ⟨761⟩—

Standard solution—Prepare a 10% w/v solution of USP Goserelin Acetate RS in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.

Test solution—Prepare a 10% w/v solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.

Procedure—Obtain a ^{13}C, proton-decoupled NMR spectrum of both the *Standard solution* and the *Test solution*. The spectra from both solutions should be qualitatively similar, and all the resonances from the spectrum of the *Standard solution* should be present in the spectrum of the *Test solution* and have the same chemical shift values; any other resonances in the spectrum of the *Test solution* should be identified.

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 –52° and –56°.

Test solution: 2 mg per mL, in water, calculated on the anhydrous and acetic acid-free basis.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 16 USP Endotoxin Units per mg of goserelin, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

Water, *Method I* ⟨921⟩**:** not more than 10.0%.

Limit of acetic acid—

Mobile phase—Transfer 49.04 g of sulfuric acid to a 1000-mL volumetric flask, dilute with water to volume, and mix. Accurately transfer 20 mL of this solution to a 2000-mL volumetric flask, dilute with water to volume, mix, filter, and degas.

Test solution—Dissolve about 20 mg of Goserelin Acetate, accurately weighed, in 2 to 3 mL of *Mobile phase*. Connect a 1-mL cartridge containing L44 packing to a 1-mL cartridge containing L2 packing, which is then attached to a suitable vacuum apparatus. With the vacuum applied, wash the cartridge combination with 2 mL of methanol followed by 15 mL of *Mobile phase,* and discard the washings. Quantitatively apply the solution containing Goserelin Acetate to the cartridge combination, and wash through the cartridge system with several small volumes of *Mobile phase*. Collect the solution and washings in a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Standard solution—Transfer 2.0 mL of glacial acetic acid to a 500-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a standard stock solution. Transfer 5.0 mL of the standard stock solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—[NOTE—Condition the column for about 24 hours until a stable baseline is obtained.] The liquid chromatograph is equipped with a 206-nm detector and a 7.8-mm × 30-cm column that contains packing L17. The column temperature is maintained at 65°, and the flow rate is about 0.8 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time is about 11 minutes for acetic acid; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3.1%.

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 percentage of acetic acid in the portion of Goserelin taken by the formula:

$$(1.049/5)(r_U / r_S)(1/W),$$

in which 1.049 is the weight per mL, in g, of glacial acetic acid; W is the sample weight of Goserelin Acetate, in g, taken to prepare the *Test solution* and corrected (for purposes of the calculation) to eliminate the water content, which is determined immediately prior to the test; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The content of acetic acid is between 4.5% and 15.0%.

Related compounds—

Mobile phase, Standard preparation, Diluted standard preparation, Resolution solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Diluted test solution—Transfer 1 mL of the *Test solution* into a 100-mL volumetric flask, and dilute with water to volume.

Procedure—Separately inject equal volumes (about 10 µL) of the *Test solution, Diluted test solution, Resolution solution,* and *System suitability solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of goserelin-related impurities in the portion of Goserelin Acetate taken by the formula:

$$r_i / r_S,$$

in which r_i is the peak area response for any individual impurity in the *Test solution;* and r_S is the peak area response of the main goserelin peak in the *Diluted test solution:* not more than 1.0% of decarbamoylgoserelin is found, not more than 0.5% of any other impurity is found, and not more than 2.5% of total impurities is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (1600 : 400 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Goserelin Acetate RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Diluted standard preparation—Transfer 1 mL of the *Standard preparation* to a 10–mL volumetric flask, and dilute with water to volume.

Assay preparation—Transfer about 25 mg of Goserelin Acetate, accurately weighed, to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Resolution solution—Dissolve the contents of a vial of USP Goserelin Related Compound A RS in water to obtain a concentration of 0.1 mg per mL, and mix with an equal volume of *Diluted standard preparation.*

System suitability solution—Dissolve the contents of a vial of USP Goserelin Validation Mixture RS with 1 mL of water.

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 3.5-µm packing L1. The column temperature is maintained between 50° and 55°, and the flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak

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responses as directed for *Procedure:* the retention time for goserelin is between 40 and 50 minutes, the relative retention times are about 0.67 for 4-D-ser-goserelin, 0.89 for decarbamoylgoserelin, 0.92 for 5-D-tyr-goserelin, 0.94 for 2-D-his-goserelin, and 1.0 for goserelin; and the resolution, *R,* between 4-D-ser-goserelin and goserelin is not less than 7.0. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* two peaks, corresponding to decarbamoylgoserelin and 2-D-his-goserelin and eluting prior to the principal peak, are visible; three peaks eluting after the principal peak are visible; the column efficiency for the principal peak is not less than 2000 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 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 goserelin ($C_{59}H_{84}N_{18}O_{14}$) in the portion of Goserelin Acetate taken (where sample weight has been corrected for water and acetic acid content, both determined immediately prior to the assay) by the formula:

$$25C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Goserelin Acetate RS in the *Standard preparation;* and r_U and r_S are the goserelin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Levothyroxine Sodium Tablets, *USP 28* page 1128 and page 55 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to clarify the calculations under the test for *Limit of liothyronine sodium*.

(PA4: E. Gonikberg) RTS—41612-1

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass. ▲▲*USP28*]

TEST 1—

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl 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⟩).

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 *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.

•TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus, Time, Standard solution, and *Test solution*—Proceed as directed for *Test 1*. [NOTE—Filter the *Standard solution* in a manner identical to the *Test solution*.]

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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 and acetonitrile (65 : 35) with 0.5 mL of phosphoric acid per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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 5-µm packing L10. The column temperature is maintained at 30°. 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 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 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.●3

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

▲NOTE—Do not use paddle stirrers with synthetic coating.▲*USP28*

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 *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.

Change to read:

Limit of liothyronine sodium—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay* under *Levothyroxine Sodium*.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Procedure—Proceed as directed in the *Assay* under *Levothyroxine Sodium*. Calculate the ~~quantity, in µg,~~

▲percentage▲*USP29*
of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$) in the portion of Tablets taken by the formula:

~~$(672.96/650.98)(10C)(r_U/r_S),$~~

$$▲(672.96/650.98)(1000C/W)(r_U/r_S),▲USP29$$

in which 672.96 and 650.98 are the molecular weights of liothyronine sodium and liothyronine, respectively; C is the concentration, in µg per mL, of USP Liothyronine RS in the *Standard solution;*

▲W is the amount, in µg, of levothyroxine sodium in the portion of Tablets, based on the label claim, taken to prepare the *Test solution;*▲*USP29*

and r_U and r_S are the liothyronine peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 2.0% of liothyronine is found.

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BRIEFING

Lidocaine Hydrochloride, *USP 28* page 1130 and page 1256 of *PF* 30(4) [July-Aug. 2004]. On the basis of comments and data received, it is proposed to remove the temperature control in the *Chromatographic system* for the *Assay.*

(PA1: K. Russo) RTS—41872-1

Change to read:

Assay—

Mobile phase—Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40. Mix about 4 volumes of this solution with 1 volume of acetonitrile, so that the retention time of lidocaine is about 4 to 6 minutes. Pass through a membrane filter having a 1-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve about 85 mg of USP Lidocaine RS, accurately weighed, with warming if necessary, in 0.5 mL of 1 N hydrochloric acid in a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 1.7 mg of lidocaine per mL.

Assay preparation—Transfer about 100 mg of Lidocaine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Resolution preparation—Prepare a solution of methylparaben in *Mobile phase* containing about 220 µg per mL. Mix 2 mL of this solution and 20 mL of the *Standard preparation.*

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. ~~and is operated at a temperature between 20° and 25°, maintained at ± 1.0° of the selected temperature.~~

▲▲*USP29*
The flow rate is about 1.5 mL per minute. Chromatograph about 20 µL of the *Resolution preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the lidocaine and methylparaben peaks is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

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 responses for the major peaks. Calculate the quantity, in mg, of $C_{14}H_{22}N_2O \cdot HCl$ in the portion of Lidocaine Hydrochloride taken by the formula:

$$(270.80/234.34)(50C)(r_U/r_S),$$

in which 270.80 and 234.34 are the molecular weights of lidocaine hydrochloride and lidocaine, respectively; C is the concentration, in mg per mL, of USP Lidocaine RS in the *Standard preparation;* and r_U and r_S are the lidocaine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Lidocaine Hydrochloride and Epinephrine Injection, *USP 28* page 1132 and page 1257 of *PF* 30(4) [July–Aug. 2004]. On the basis of comments and data received, it is proposed to remove the temperature control in the *Chromatographic system* for the *Assay for lidocaine hydrochloride* and the *Assay for epinephrine.*

(PA1: K. Russo) RTS—41872-2

Change to read:

Assay for lidocaine hydrochloride—

Mobile phase—Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40. Mix about 4 volumes of this solution with 1 volume of acetonitrile, so that the retention time of lidocaine is about 4 to 6 minutes. Pass through a membrane filter having a 1-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve about 85 mg of USP Lidocaine RS, accurately weighed, with warming if necessary, in 0.5 mL of 1 N hydrochloric acid in a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 1.7 mg of lidocaine per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 100 mg of lidocaine hydrochloride, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Resolution preparation—Prepare a solution of methylparaben in *Mobile phase* containing about 220 µg per mL. Mix 2 mL of this solution and 20 mL of the *Standard preparation*.

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. ~~and is operated at a temperature between 20° and 25° maintained at ± 1.0° of the selected temperature.~~

▲▲*USP29*
The flow rate is about 1.5 mL per minute. Chromatograph about 20 µL of the *Resolution preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between lidocaine and methylparaben is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

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 responses for the major peaks. Calculate the quantity, in mg, of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$) in each mL of the Injection taken by the formula:

$$(270.80/234.34)(50)(C/V)(r_U/r_S),$$

in which 270.80 and 234.34 are the molecular weights of lidocaine hydrochloride and lidocaine, respectively; C is the concentration, in mg per mL, of USP Lidocaine RS in the *Standard preparation;* V is the volume, in mL, of Injection taken; and r_U and r_S are the lidocaine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Change to read:

Assay for epinephrine—

Mobile phase—Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40. Dissolve 1.1 g of sodium 1-heptanesulfonate in this solution, add 1.0 mL of 0.1 M edetate disodium, and mix. Mix about 9 volumes of this solution with 1 volume of methanol, so that the retention time of epinephrine is about 4 to 6 minutes. Pass through a membrane filter having a 1-µm or finer porosity, and degas.

Standard preparation—Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in *Mobile phase* to obtain a solution having a known concentration of about 9 µg of epinephrine bitartrate per mL. Pipet 10 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 1.8 µg of epinephrine bitartrate per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 50 µg of epinephrine, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is fitted with a 3.9-mm × 30-cm stainless steel column packed with packing L1 and is equipped with an electrochemical detector held at a potential of +650 mV, a controller capable of regulating the background current, and a suitable recorder. ~~and it is operated at a temperature between 20° and 25° maintained at ± 1.0° of the selected temperature.~~

▲▲*USP29*

The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the relative standard deviation of the peak responses of successive injections of the *Standard preparation* is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph by means of a suitable microsyringe or sampling valve, adjusting the specimen size and other operating parameters such that satisfactory chromatography and peak responses are obtained. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of epinephrine ($C_9H_{13}NO_3$) in each mL of the Injection taken by the formula:

$$(183.21/333.30)(50)(C/V)(r_U/r_S),$$

in which 183.21 and 333.30 are the molecular weights of epinephrine and epinephrine bitartrate, respectively; C is the concentration, in µg per mL, of USP Epinephrine Bitartrate RS in the *Standard preparation; V* is the volume, in mL, of Injection taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Lipid Injectable Emulsion, page 421 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to revise the Definition and the *Packaging and storage* sections. In addition, it is proposed to add a new section, *Globule size limits,* that consists of *Method I* and *Method II* as described in *Method I—Light-Scattering Method* and *Method II—Light Obscuration or Extinction Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩, in *PF* 30(6), page 2235. *Method I* uses a light-scattering technique to determine the mean droplet diameter, and *Method II* uses a light-obscuration method to determine the size distribution of globules in the large-diameter tail of the dispersion.

(PPI: J. Kelly) RTS—41318-1

Add the following:

▲Lipid Injectable Emulsion

» ~~Lipid Injectable Emulsion is a sterile 10 percent, 20 percent, or 30 percent w/v oil-in-water emulsion in a vehicle containing glycerol in Water for Injection. The oils are Soybean Oil, Safflower Oil, Olive Oil, Medium-Chain Triglycerides, or other suitable nutritional oils, or a mixture of these oils. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the oil. It contains no antimicrobial agents. It contains Egg Phospholipids as an emulsifying agent.~~ Lipid Injectable Emulsion used in total parenteral nutrition is a sterile 10 percent (0.10 g per mL), 20 percent (0.20 g per mL), or 30 percent (0.3 g per mL) w/v emulsion in a vehicle. The vehicle con-

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tains 2.25 percent to 2.5 percent w/v Glycerin and 0.6 percent to 1.8 percent w/v parenteral Egg Phospholipids in Water for Injection. The principal oil used is Soybean Oil, which provides an ample supply of the essential fatty acids: linoleic acid and linolenic acid. Other oils such as Safflower Oil, Medium-Chain Triglycerides, Olive Oil, Fish Oil Containing Omega-3 Acids, or other suitable oils, can be mixed with Soybean Oil. Hence, Soybean Oil can be the only oil or be part of a mixture containing other oils. It contains not less than 90 percent and not more than 110 percent of the labeled amount of each of the defined oils. It contains no antimicrobial agents. The final products are terminally sterilized.

Packaging and storage~~— Preserve in a single-dose, glass container or glass *Pharmacy Bulk Package* (see *Injections* ⟨1⟩). Use elastomeric closures that are compatible with both the oil and water phases of the Emulsion. Store at controlled room temperature, and protect from freezing.~~ Preserve in single-dose Type I or Type II glass container or glass *Pharmacy Bulk Package* (see *Injections* ⟨1⟩). Use elastomeric closures that are compatible with both the oil and water phases of the Emulsion. Store at a temperature not below 4° (protect from freezing) or above 30° (protect from excessive heat).

Labeling—The label states the identity and the quantities of the oils in the Emulsion. The label states the total ~~osmolal~~ osmolar concentration (or osmolarity) in ~~mOsmol~~ mOsm per ~~kg.~~ L. The labeling provides the following information: do not use if there is evidence of excessive creaming or aggregation, if free oil droplets are visible, or if there ~~are other forms of phase separation indicating that the stability of the product has been compromised.~~ are other indications of compromised integrity such as microbial growth present in the product.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Particle Count RS.*

Fatty acid composition—Transfer a volume of the Emulsion, equivalent to about 200 mg of lipids, to a stoppered extraction vessel, add 10 mL of ether, and mix. Add 5 g of anhydrous sodium sulfate, mix, and allow the mixture to stand until separation of the layers is complete. Wet the packing of a chromatographic silica cartridge with a few mL of ether, transfer about 5 mL of the ether layer from the extraction vessel to the column reservoir, and elute at a rate of between 5 and 10 drops per minute into a suitable vessel. Evaporate the ether from the eluant, and dissolve the residue in 5.0 mL of toluene. Transfer 1.0 mL of the toluene solution to a reaction vial, and add 0.4 mL of (*m*-trifluoromethylphenyl) trimethylammonium hydroxide in methanol. Cover, mix, and allow to stand for 30 minutes. Inject about 1 µL of this solution into a ~~gas ionization detector and~~ gas chromatograph with a 0.53-mm × 50-m wide-bore, fused-silica capillary column coated with a 2.0-µm thickness of liquid phase G16 and maintained at a temperature of 200°. Helium is used as the carrier gas at a flow rate of about 10 mL per minute. Measure the five main peak areas of the methyl esters of the fatty acids. The order of elution is palmitate, stearate, oleate, linoleate, and linolenate: their relative peak areas expressed as a percentage of the five main peaks are in the known ranges for the oils or mixtures of oils specified on the label.

Bacterial endotoxins ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mL.

pH ⟨791⟩**:** between 6.0 and 9.0

Globule size limits—Lipid Injectable Emulsion meets the requirements of the limits specified in both *Method I* and *Method II* as directed under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩.

Limit of oil droplet mean diameters (See *Method I—Light Scattering Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light scattering, determine the mean droplet diameter (MDD): the sample meets the requirements.

Limit of large globule volume-diameter (See *Method II—Light Obscuration or Extinction Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light obscuration, determine the size distribution of globules in the large-diameter tail of the dispersion (detection threshold ≥2.0 μm). Calculate the volume-weighted mass of lipid in the form of globules with diameters in excess of 5.0 μm per 100 mL of Emulsion. This mass does not exceed 0.05% of the dispersed phase that is > 5.0 μm from the nominal lipid concentration stated on the label.

~~**Particulate matter** ⟨788⟩**:** meets the requirements for *Large-Volume Injections* for single-dose infusion.~~

Limit of free fatty acid—

Solvent—Prepare a mixture of heptane, isopropanol, and water (400 : 400 : 200) in a separatory funnel. Allow the phases to separate, and discard the lower phase. Filter the upper phase (heptane solution) through 40 g of anhydrous sodium sulfate. Store in a tightly-capped glass container, and use within 1 week.

Chromatographic column—Prepare a slurry of heptane and chromatographic silica gel having an average pore size of 6 nm, and activate at 110° for not less than 1 hour prior to use. Transfer the slurry to a 2.3-cm chromatographic tube (see *Column Chromatography* under *Chromatography* ⟨621⟩), and pack to a bed height of between 5 and 6 cm. Wash the column with about 40 mL of heptane, and drain the heptane through the column to a level of about 0.5 cm above the silica gel bed.

Procedure—Transfer 20.0 mL of the Emulsion to a flask, freeze, and lyophilize. Dissolve the residue in 3 mL of *Solvent,* and transfer the solution to the column. Rinse the flask with three 30-mL portions of *Solvent,* and transfer the washings to the column, allowing each rinsing to drain to the top of the column bed before applying the next rinse. Collect a total of 120 mL of effluent. Add 10 drops of phenolphthalein TS to the effluent, bubble nitrogen through the solution, and titrate with 0.02 N alcoholic potassium hydroxide VS until the solution remains pale pink after mixing for 10 seconds. Titrate a blank using 120 mL of *Solvent.* Calculate the quantity of free fatty acids, in mEq, in the portion of Emulsion taken by the formula:

$$(V_U - V_B)N/20C,$$

in which V_U is the volume, in mL, of the 0.02 N alcoholic potassium hydroxide consumed by the eluant; V_B is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the blank; N is the normality of the 0.02 N alcoholic potassium hydroxide; and C is the labeled concentration of the sum of the individual oils in the Emulsion: not more than 0.07 mEq of free fatty acids per mL of Emulsion is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of isopropanol, ethyl acetate, and glacial acetic acid (179 : 20 : 1).

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Standard preparation—Dissolve an accurately weighed portion of Soybean Oil (or other relevant oils used in the Emulsion) in *Mobile phase* to obtain a solution having a known concentration of about 8 mg per mL.

Assay preparation—Transfer an accurately measured portion of Emulsion, equivalent to about 800 mg of oil, to a suitable container, and freeze-dry. Dissolve the residue in *Mobile phase,* and quantitatively transfer to a 100-mL volumetric flask with the aid of additional portions of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix to obtain a solution containing about 8 mg of oil per mL.

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 packing L21. The flow rate is about 1 mL per minute, adjusted so that the peak due to oil elutes at about 6.5 minutes. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 1.0; the tailing factor for the oil peak 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 50 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 oil in the portion of Emulsion taken by the formula:

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

~~in which C is the concentration, in mg per mL, of Soybean Oil in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~ in which C is the concentration, in mg per mL, of Soybean Oil or other relevant oils used in the Emulsion in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Magnesium Carbonate and Citric Acid for Oral Solution, *USP 28* page 1167—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩. Other changes are editorial.

(PA4: E. Gonikberg ; D. Bempong) RTS—42196-8

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Content of anhydrous citric acid—

~~*Cation-exchange column*—Mix 10 g of styrene divinylbenzene cation-exchange resin with 50 mL of water in a beaker. Allow the resin to settle, and decant and discard the supernatant until a slurry of resin remains. Pour the slurry into a 15-mm × 30-cm glass chromatographic tube having a pledget of glass wool in the bottom and a stopcock, and allow to settle as a homogeneous bed. Place a pledget of glass wool on the top of the bed. Wash the resin bed with about 100 mL of water, closing the stopcock when the water level has just entered the glass wool pledget on the surface above the resin bed.~~

~~*Test solution*—Transfer an accurately measured volume of the constituted Oral Solution, equivalent to about 9 g of anhydrous citric acid, to a 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Transfer 5.0 mL of the *Test solution* carefully onto the top of the resin bed in the cation-exchange column. Place a 250-mL volumetric flask below the column, open the stopcock, and allow to flow until the solution has entered the resin bed. Elute the column with 70 mL of water at a rate of about 5 mL per minute, collecting the eluate in a beaker. Boil the eluate for 1 minute, cool, and add 5 drops of phenolphthalein TS. Titrate with 0.1 N sodium hydroxide VS to a pink endpoint. Each mL of 0.1 N sodium hydroxide is equivalent to 6.404 mg of anhydrous citric acid ($C_6H_8O_7$). The content of anhydrous citric acid is between 76.6% and 107.8% of the labeled amount of magnesium citrate.~~

~~NOTE—Perform the following tests on the Oral Solution obtained after constitution as directed in the labeling. Accurately measure the volume of the constituted Oral Solution.~~

In-Process Revision

▲*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of the constituted Oral Solution, equivalent to about 9 g of anhydrous citric acid into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of constituted Oral Solution taken by the formula:

$$0.001(192.12 / 189.10)C_S D(r_U/r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively. The content of anhydrous citric acid is between 76.6% and 107.8% of the labeled amount of magnesium citrate.▲*USP29*

(Official January 1, 2009)

Change to read:

Other requirements—

▲Constitute Magnesium Carbonate and Citric Acid for Oral Solution as directed in the labeling:▲*USP29*
it responds to the *Identification* tests and meets the requirements for *Chloride, Sulfate,* and *Tartaric acid* under *Magnesium Citrate Oral Solution*.

(Official January 1, 2009)

BRIEFING

Magnesium Chloride, *USP 28* page 1168 and page 893 of *PF* 30(3) [May–June 2004]. It is proposed to clarify that the limit under the test for *Insoluble matter* is 0.005%, and to delete the redundant second requirement for the actual weight of the residue.

(PA4: E. Gonikberg) RTS—42165-1

Change to read:

Identification—A solution (1 in 20) responds to the tests for *Magnesium* ⟨191⟩ and for *Chloride* ⟨191⟩.

■[NOTE—When performing the test for *Chloride,* acidify the sample solution with dilute nitric acid prior to adding 6 N ammonium hydroxide.]■1S *(USP28)*

Change to read:

Insoluble matter—Dissolve 20 g, accurately weighed, in 200 mL of water, heat to boiling, and digest in a covered beaker on a steam bath for 1 hour. Filter through a tared filtering crucible, wash thoroughly, ~~and~~

▲▲*USP29*
dry at 115°,

▲and determine▲*USP29*
the weight of the residue: ~~does not exceed 1 mg (0.005%).~~

▲not more than 0.005% is found.▲*USP29*

BRIEFING

Magnesium Citrate Oral Solution, *USP 28* page 1169—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(PA4: E. Gonikberg; D. Bempong) RTS—42196-7

In-Process Revision

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Assay for anhydrous citric acid— ~~Measure accurately 10 mL of Oral Solution, which previously has been freed from excessive carbon dioxide by repeated pouring, into a 250-mL beaker, and add 30 mL of water. Then add phenolphthalein TS and just enough 1 N sodium hydroxide to give the liquid a persistent pink color, and acidify with 4 drops of 1 N hydrochloric acid. Add 20 mL of calcium chloride TS, and concentrate, by boiling, to about 30 mL, stirring constantly with a rubber-tipped glass rod during the boiling. Completely transfer the precipitate from the hot mixture to a filter of from 9 cm to 11 cm in diameter with the aid of small quantities of boiling water, then wash the precipitate five times with boiling water. Collect the filtrate and washings in a 150-mL beaker, and concentrate the solution, by boiling, to about 20 mL. Add sufficient 6 N ammonium hydroxide, dropwise, to give the liquid a distinct red color, and then concentrate to about 10 mL. Transfer the precipitate completely from the hot mixture to a filter of from 7 cm to 9 cm in diameter with the aid of small quantities of boiling water, and wash the precipitate six times with 5-mL portions of boiling water.~~

~~Dry the two filters with the precipitates, and incinerate them together in a loosely covered platinum crucible, heating first at a low temperature until the precipitates are well charred, and then removing the cover and raising the temperature until the residue is nearly white. If a gas flame is used, prevent its contact with the mass in the crucible. Cool, place the crucible with its contents in a suitable beaker, and add about 30 mL of water and then 50.0 mL of 0.5 N hydrochloric acid VS. When the residue has dissolved, remove the crucible, rinsing it well with water into the beaker. Add 100 mL of water, cover the beaker with a watch glass, and boil gently for 10 minutes. Cool, and titrate the excess acid with 0.5 N sodium hydroxide VS, using phenolphthalein TS as the indicator. Each mL of 0.5000 N hydrochloric acid is equivalent to 32.02 mg of $C_6H_8O_7$.~~

▲*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Measure accurately 10 mL of Oral Solution that previously has been freed from excessive carbon dioxide by repeated pouring, into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of Oral Solution taken by the formula:

$$0.001(192.12/189.10)C_sD(r_U/r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_s is the concentration, in µg per mL, of citrate in *Standard Preparation 1;D* is the dilution factor; and r_U and r_s are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1*, respectively.▲*USP29*

(Official January 1, 2009)

BRIEFING

Magnesium Citrate for Oral Solution, *USP 28* page 1170—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩. Other changes are editorial.

(PA4: E. Gonikberg; D. Bempong) RTS—42196-6

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Content of anhydrous citric acid—

~~*Cation-exchange column, Test solution,* and *Procedure*—Proceed as directed in the test for *Content of anhydrous citric acid* under *Magnesium Carbonate and Citric Acid for Oral Solution*. The content of anhydrous citric acid is between 76.6% and 93.7% of the labeled amount of magnesium citrate.~~

In-Process Revision

~~NOTE—Perform the following tests on the Oral Solution obtained after constitution as directed in the labeling. Accurately measure the volume of the constituted Oral Solution.~~

▲*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of the constituted Oral Solution, equivalent to about 9 g of anhydrous citric acid into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of constituted Oral Solution taken by the formula:

$$0.001(192.12 / 189.10)C_S D(r_U / r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively. The content of anhydrous citric acid is between 76.6% and 93.7% of the labeled amount of magnesium citrate.▲*USP29*

(Official January 1, 2009)

Change to read:

Other requirements—

▲Constitute Magnesium Citrate for Oral Solution as directed in the labeling:▲*USP29*
it responds to the *Identification* tests and meets the requirements for *Chloride, Sulfate,* and *Tartaric acid* under *Magnesium Citrate Oral Solution*.

(Official January 1, 2009)

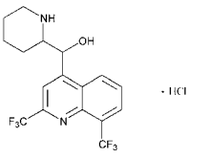
BRIEFING

Mefloquine Hydrochloride, page 1260 of *PF* 30(4) [July–Aug. 2004]. It is proposed to revise the test for *Related compounds* to more accurately reflect the USP Reference Standard used in the *System suitability solution*.

(PA7b: B. Davani) RTS—42239-1

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. USP Mefloquine Related Compound A RS.*

In-Process Revision

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of 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%.

Change to read:

Related compounds—

Mobile phase—Dissolve 1 g of tetraheptylammonium bromide in a mixture of a 1.5 g per L solution of sodium hydrogen sulfate, acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about ~~8 mg~~ 4 mg of USP Mefloquine Hydrochloride RS and ~~8 mg~~ 4 mg of ~~quinidine sulfate~~ USP Mefloquine Related Compound A RS to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. [NOTE—Mefloquine related compound A is *threo*-mefloquine.] 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~~ ▲0.7$_{▲USP29}$ for ~~quinidine~~ ▲mefloquine related compound A$_{▲USP29}$ and 1.0 for mefloquine; the resolution, *R,* between ~~quinidine~~ mefloquine related compound A and mefloquine is not less than ~~8.5~~ 2.0; and the relative standard deviation for replicate injections is not more than ~~3%~~ 2.0%.

Procedure—Equilibrate the column with *Mobile phase* at a flow rate of about ~~2 mL~~ 0.8 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%) the main peak in the chromatogram of the *Diluted test solution.* The response of ~~any~~ the mefloquine related compound A 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 chro-

matogram of the *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 $C_{17}H_{16}F_6N_2O \cdot HCl$.■1S *(USP28)*

BRIEFING

Mesalamine, *USP 28* page 1220. It is proposed to correct the flow rate of the carrier gas in the *Related compounds, Test 2* to 15 mL per minute for the compounds of interest to elute within the temperature program time specified in the monograph.

(PA2: D. Bempong) RTS—42053-1

Change to read:

Related compounds—

TEST 1 *(for 3-aminosalicylic acid and other related impurities)*—[NOTE—Use *Test 1* to measure 3-aminosalicylic acid and other related impurities not measured in *Test 2*.]

Mobile phase—Dissolve 1.36 g of monobasic potassium phosphate and 2.2 g of sodium 1-octanesulfonate in 890 mL of water, and adjust with phosphoric acid to a pH of 2.2. Pass through a filter having 0.5-µm or finer porosity. To the filtrate add 80 mL of methanol and 30 mL of acetonitrile. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Mesalamine RS and 3-aminosalicylic acid quantitatively in *Mobile phase* to obtain a solution having known concentrations of about 1 µg of each per mL.

Test solution—Transfer about 50 mg of Mesalamine, accurately weighed, to a 100-mL volumetric flask, add about 75 mL of *Mobile phase,* and sonicate briefly 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 × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for mesalamine and 1.3 for 3-aminosalicylic acid; and the resolution, *R,* between mesalamine and 3-aminosalicylic acid is not less than 2.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a period of time that is three times the retention time of mesalamine, and measure the peak area responses. Calculate the percentage of 3-aminosalicylic acid by the formula:

$$0.2C_3(r_3 / r_{S3}),$$

in which C_3 is the concentration, in µg per mL, of 3-aminosalicylic acid in the *Standard solution;* r_3 is the response of the 3-aminosalicylic acid peak in the chromatogram obtained from the *Test solution;* and r_{S3} is the response of the 3-aminosalicylic acid peak in the chromatogram obtained from the *Standard solution.* Calculate the percentage of each other impurity by the formula:

$$0.2C_m(r_i / r_{Sm}),$$

in which C_m is the concentration, in µg per mL, of USP Mesalamine RS in the *Standard solution;* r_i is the response of the individual impurity peak in the chromatogram obtained from the *Test solution;* and r_{Sm} is the response of the mesalamine peak in the chromatogram obtained from the *Standard solution:* not more than 0.2% of 3-aminosalicylic acid is found; not more than 0.2% of any other impurity, expressed in terms of mesalamine equivalent, is found; and the total of all impurities found is not more than 1.0%.

TEST 2 *(for aniline, 2-aminophenol, and 4-aminophenol)*—

Standard solution—Prepare a solution of aniline, 2-aminophenol, and 4-aminophenol in methanol having concentrations of 0.05, 2, and 2 mg per mL, respectively, and dilute quantitatively and stepwise, if necessary, with methylene chloride to obtain a solution having known concentrations of 0.5, 20, and 20 µg per mL, respectively.

Test solution—Mix 1.0 g of Mesalamine with 10.0 mL of methylene chloride. Allow to settle, and use the clear methylene chloride solution as the *Test solution*.

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 2.65-µm film of stationary phase G27. The carrier gas is helium flowing at a rate of ~~1.5 mL~~

▲15 mL▲*USP29*

per minute. The injection port and the detector temperatures are maintained at about 280° and 300°, respectively. The column temperature is programmed according to the following steps: the starting column temperature is 70°; after injection it is held at 70° for 2 minutes, then increased to 150° at a rate of 30° per minute, then held for 1 minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for aniline, 0.9 for 2-aminophenol, and 1.0 for 4-aminophenol; and the peaks are baseline separated.

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 peak area responses. Identify by retention time any peaks present in the chromatogram of the *Test solution* that correspond to those in the chromatogram obtained from the *Standard solution.* Calculate the quantities, in µg per g, of aniline, 2-aminophenol, and 4-aminophenol in the portion of Mesalamine taken by the formula:

$$10C(r_a / r_{Sa}),$$

in which C is the concentration, in µg per mL, of the relevant analyte in the *Standard solution;* r_a is the response of the relevant analyte in the chromatogram obtained from the *Test solution;* and r_{Sa} is the response of the relevant analyte in the chromatogram obtained from the *Standard solution:* not more than 5 µg of aniline, 200 µg of 2-aminophenol, and 200 µg of 4-aminophenol per g are found.

In-Process Revision

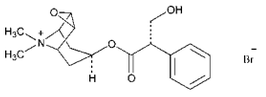
BRIEFING

Methscopolamine Bromide, page 899 of *PF* 30(3) [May–June 2004]. On the basis of comments received, it is proposed to add a test for *Chromatographic purity.* In the *Assay,* it is also proposed to replace the HPLC method with the same new stability-indicating liquid chromatographic procedure proposed for the *Chromatographic purity* test. This method is based on analyses performed with the Chromolith Performance RP-18e brand of L1 column. The typical retention time for methscopolamine bromide is about 2.4 minutes. In addition, the molecular weight of methscopolamine bromide is revised to reflect the current atomic weight values published in *USP 28.*

(PA4: E. Gonikberg) RTS—41998-1

Add the following:

▲Methscopolamine Bromide



$C_{18}H_{24}BrNO_4$ ~~398.30~~ 398.29

3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-, bromide, [7(*S*)-(1α,2*β*,4*β*,5α,7*β*]-.

6*β*,7*β*-Epoxy-3α-hydroxy-8-methyl-1α*H*,5α*H*-tropanium bromide (–)-tropate [*155-41-9*].

» Methscopolamine Bromide contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{24}BrNO_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at room temperature.

USP Reference standards ⟨11⟩**—***USP Methscopolamine Bromide RS. USP Scopolamine Hydrobromide RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: A solution (1 in 20) meets the requirements of the tests for *Bromide* ⟨191⟩.

Specific rotation ⟨781⟩**:** between –21° and –25°, ~~calculated on the dried basis,~~ determined in a solution containing 500 mg in each 10 mL.

Loss on drying ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 2.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chromatographic purity—

Buffer solution, Solution A, and *Solution B*—Proceed as directed in the *Assay.*

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

Diluted standard solution—Dilute 5 µL of the *Standard solution* with *Solution A* to 10.0 mL.

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

Scopolamine hydrobromide solution—Dissolve an accurately weighed quantity of USP Scopolamine Hydrobromide RS in *Solution A* to obtain a solution having a known concentration of about 0.05 mg per mL.

System suitability solution—Dissolve about 50 mg of USP Methscopolamine Bromide RS in *Solution A,* add 1.0 mL of *Scopolamine hydrobromide solution,* and dilute with *Solution A* to 50.0 mL. This solution contains about 0.1% of scopolamine hydrobromide.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* In addition, chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between methscopolamine and scopolamine is not less than 1.5; and the tailing factor for the methscopolamine peak is not more than 2.0.

In-Process Revision

Procedure—Separately inject equal volumes (about 5 µL) of the *Diluted standard solution* and the *Test solution* into the chromatograph, record the chromatogram for four times the retention time of methscopolamine, and measure the responses for the major peaks. Disregard any peak with an area less than that of the methscopolamine peak in the chromatogram obtained from the *Diluted standard solution,* and disregard any peak that is due to *Solution A*. Calculate the percentage of each impurity in the portion of Methscopolamine Bromide taken by the formula:

$$100F(r_i / r_S),$$

in which F is the relative response factor for the methscopolamine bromide impurities (see *Table 1*); r_i is the peak area of any impurity obtained from the *Test solution;* and r_S is the peak area of methscopolamine obtained from the chromatogram of the *Test solution*: not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

Table 1.

Name	Relative Retention Time	Relative Response Factor (*F*)
Tropic acid	0.4	0.4
Scopolamine hydrobromide	0.9	1.0
Methylatropine bromide	1.2	1.0
Apomethscopolamine bromide	3.5	0.6
Any other impurity	—	1.0

Assay—

~~*Mobile phase*—Prepare a solution containing 2.6 g of decyl sodium sulfate, in 450 mL of water. Add 550 mL of methanol, adjust with 1 N sulfuric acid to a pH of 3.5, mix, filter, and degas.~~

~~*Standard preparation*—Transfer about 25 mg of USP Methscopolamine Bromide RS, accurately weighed, to a 100 mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

~~*Assay preparation*—Prepare as directed under the *Standard preparation,* using about 25 mg of Methscopolamine Bromide, accurately weighed.~~

~~*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. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for the peak responses is not greater than 2.0%.~~

~~*Procedure*—Separately inject a volume (about 50 µL) of the *Standard preparation* and the *Assay preparation* into a chromatograph, record the chromatogram, and measure the peak responses. Calculate the quantity, in mg, of $C_{18}H_{24}BrNO_4$ in the portion of Methscopolamine Bromide taken by the formula:~~

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

~~in which C is the concentration, in mg per mL, of USP Methscopolamine Bromide RS in the *Standard preparation;* and r_U and r_S are the peak responses of the methscopolamine bromide obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

In-Process Revision

Buffer solution—Prepare a solution containing 5.16 g of sodium 1-hexanesulfonate monohydrate and 3.40 g of monobasic potassium phosphate in 1000 mL of water, adjust with 1 M phosphoric acid to a pH of 2.8, and mix.

Solution A—Mix 850 mL of *Buffer solution* and 150 mL of acetonitrile, filter, and degas.

Solution B—Mix 500 mL of *Buffer solution* and 500 mL of acetonitrile, 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⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Methscopolamine Bromide RS in *Solution A* to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Transfer about 50 mg of Methscopolamine Bromide, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 10-cm column that contains packing L1. The flow rate is about 3 mL per minute. The column temperature is maintained at 50°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3	100	0	isocratic
3–10	100→85	0→15	linear gradient
10–10.1	85→100	15→0	linear gradient
10.1–13	100	0	re-equilibration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six replicate injections is not greater than 1%.

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 peak area responses. Calculate the quantity, in mg, of $C_{18}H_{24}BrNO_4$ in the portion of Methscopolamine Bromide taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Methscopolamine Bromide RS in the *Standard preparation;* and r_U and r_S are the peak area responses of methscopolamine obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Methscopolamine Bromide Tablets. On the basis of a recent request, it is proposed to reinstate this monograph, which was omitted from *USP 23–NF 18* in 1995. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Phenomenex Bondclone brand of L1 column. The typical retention time for the methscopolamine peak is about 23 minutes. The liquid chromatographic procedure in the *Dissolution* test is based on analyses performed with the Phenomenex Synergi Hydro-RP 80A brand of L1 column. The typical retention time for the methscopolamine peak is about 4.8 minutes.

(PA4: E. Gonikberg; BPC: M. Marques) RTS—41016-1; 41016-2; 41016-3; 41016-4

Add the following:

▲Methscopolamine Bromide Tablets

» Methscopolamine Bromide Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of methscopolamine bromide ($C_{18}H_{24}BrNO_4$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Methscopolamine Bromide RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

pH 7.3 Dye-buffer solution—Prepare a solution containing, in each 500 mL, 200 mg of bromothymol blue, 3.2 mL of 0.1 N sodium hydroxide, 577.5 mg of citric acid monohydrate, and 6.3 mg of anhydrous dibasic sodium phosphate.

Test solution—Finely powder 1 Tablet, and transfer an amount, equivalent to about 0.5 mg of methscopolamine bromide, to a suitable container. Add 20 mL of water, heat for 5 minutes on a steam bath with frequent agitation, and centrifuge to obtain a clear supernatant. Transfer 10 mL of the supernatant to a vessel containing 10 mL of chloroform and 10 mL of *pH 7.3 Dye-buffer solution*. Shake vigorously for 3 minutes, centrifuge, and transfer 8 mL of the chloroform layer to a suitable container. Evaporate to dryness, and dissolve the residue in 1 mL of chloroform.

Standard solution—Prepare a solution in water containing about 0.025 mg of USP Methscopolamine Bromide RS per mL, and treat as directed above, beginning with "Transfer 10 mL of the supernatant."

Application volume: 50 µL.

Developing solvent system—In a suitable container, mix water, butyl alcohol, and glacial acetic acid (5: 4 : 1), then transfer a measured volume of the upper organic layer to a suitable container, and mix with a volume of alcohol equivalent to 20% of the volume of the organic layer.

Procedure—Allow the solvent front to move about three-fourths of the length of the plate, remove the plate from the developing chamber, mark the solvent front, and dry the plate under a current of air for 30 minutes. Spray the plate evenly with potassium–bismuth iodide TS: the chromatogram of the *Test solution* shows a bright orange spot on a yellow background corresponding in R_F value (about 0.25) to that in the chromatogram obtained from the *Standard solution*. [NOTE—Bromothymol blue produces a dark yellow spot at an R_F value of about 0.8.]

B: Powder a number of Tablets, equivalent to about 5 mg of methscopolamine bromide, digest with 5 mL of water for 10 minutes, and filter: a portion of the clear solution so obtained responds to the test for *Bromide* ⟨191⟩.

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the percentage of the labeled amount of methscopolamine bromide dissolved using the following method.

pH 3.0 Phosphate buffer—Dissolve 5.44 g of monobasic potassium phosphate in 1 L of water. Adjust with 1 N phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.0 Phosphate buffer* and methanol (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

In-Process Revision

Standard solution—Dissolve an accurately weighed quantity of USP Methscopolamine Bromide RS in *Medium*, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution*.

Test solution—Use portions of the solution under test that have been passed through a 0.45-µm PTFE filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 204-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. 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 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 responses for the major peaks. Calculate the percentage of methscopolamine bromide dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times LC},$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Methscopolamine Bromide RS in the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the factor for conversion to percentage; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{18}H_{24}BrNO_4$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay—

Mobile phase—Prepare a solution containing 2.6 g of decyl sodium sulfate, in 450 mL of water. Add 550 mL of methanol, adjust with 1 N sulfuric acid to a pH of 3.5, mix, filter, and degas.

Standard preparation—Transfer about 25 mg of USP Methscopolamine Bromide RS, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—

FOR THE TABLETS THAT CONTAIN 2.5 MG OF METHSCOPOLAMINE BROMIDE—Place 10 Tablets in a 100-mL volumetric flask, add about 50 mL of *Mobile phase*, and sonicate for 30 minutes. Shake by mechanical means for 30 minutes, dilute with *Mobile phase* to volume, and mix. Pass a portion through a 0.45-µm PTFE filter, discarding the first 2 to 3 mL of the filtrate.

FOR THE TABLETS THAT CONTAIN 5 MG OF METHSCOPOLAMINE BROMIDE—Place 10 Tablets in a 200-mL volumetric flask, add about 100 mL of *Mobile phase,* and sonicate for 30 minutes. Shake by mechanical means for 30 minutes, dilute with *Mobile phase* to volume, and mix. Pass a portion through a 0.45-µm PTFE filter, discarding the first 2 to 3 mL of the 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 packing L1. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not greater than 2.0%.

Procedure—Separately inject a volume (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatogram, and measure the

peak responses. Calculate the quantity, in mg, of methscopolamine bromide ($C_{18}H_{24}BrNO_4$) 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 Methscopolamine Bromide RS in the *Standard preparation;* and r_U and r_S are the peak responses of the methscopolamine bromide obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

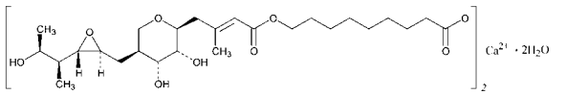
Mupirocin Calcium; Mupirocin Cream. Because there are no existing *USP* monographs for this active antibiotic drug substance and dosage form, new monographs are being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Zorbax C8 brand of L7 column. In the test for *Related compounds,* typical retention times for pseudomonic acid D and mupirocin are about 9 minutes and 12 minutes, respectively. In the *Assay,* typical retention times for pseudomonic acid D and mupirocin are 7 minutes and 9 minutes, respectively.

(PA7: L. Callahan) RTS—37476-1; 41278-1

In-Process Revision

Add the following:

▲Mupirocin Calcium



$C_{52}H_{86}CaO_{18} \cdot 2H_2O$ 1075.34

Nonanoic acid, 9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-[[3-(2-hydroxy-1-methylpropyl)oxiranyl]-methyl]-2*H*-pyran-2-yl]-2-butenyl]oxy-, calcium salt (2 : 1), dihydrate, [2*S*-[2α(*E*),3β,4β,5α[2*R**,3*R**-(1*R**,2*R**)]]].

(α*E*,2*S*,3*R*,4*R*,5*S*)-5-[(2*S*,3*S*,4*S*,5*S*)-2,3-Epoxy-5-hydroxy-4-methylhexyl]tetrahydro-3,4-dihydroxy-β-methyl-2*H*-pyran-2-crotonic acid, ester with 9-hydroxynonanoic acid, calcium salt (2 : 1), dihydrate [*115074-43-6*].

» Mupirocin Calcium contains the equivalent of not less than 865 µg and not more than 936 µg of mupirocin ($C_{26}H_{44}O_9$) per mg.

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Mupirocin Calcium RS. USP Mupirocin Lithium RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—[NOTE—Do not dry or grind extensively.]

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 20 µg per mL.

Medium: methanol.

C: When moistened with hydrochloric acid, it meets the requirements of the flame test for *Calcium* ⟨191⟩.

Crystallinity ⟨695⟩**:** meets the requirement.

Specific rotation ⟨781S⟩**:** between –16° and –20°.

Test solution: 50 mg per mL, in methanol.

Water, *Method I* ⟨921⟩**:** not less than 3.0% and not more than 4.5%.

Chloride ⟨221⟩—Dissolve 50 mg in a mixture of 1 mL of 2 N nitric acid and 15 mL of methanol. Add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 0.70 mL of 0.020 N hydrochloric acid (0.5%).

Related compounds—

0.1 M Ammonium acetate—Prepare as directed in the *Assay*.

Mobile phase—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

pH 4 Acetate buffer—Transfer about 13.6 g of sodium acetate to a 1000-mL volumetric flask, and dissolve in about 900 mL of water. Adjust with glacial acetic acid to a pH of 4.0, and dilute with water to volume.

Diluent—Prepare a mixture of *pH 4 Acetate buffer* and methanol (1 : 1).

Standard solution—Transfer about 25 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 50 mg of Mupirocin Calcium, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Resolution solution—Adjust 10 mL of the *Standard solution* with 6 N hydrochloric acid to a pH of 2.0, allow to stand for 20 hours, and adjust with 5 N sodium hydroxide to a pH of 4.0.

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 7-µm packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the second of two peaks corresponding to hydrolysis products and the peak corresponding to mupirocin is not less than 7.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 (6 minutes) for pseudomonic acid D and 1.0 (14 minutes) for mupirocin; the column efficiency for the mupirocin peak is not less than 3000 theoretical plates; the tailing factor for the mupirocin peak is not more than 2; and the relative standard deviation of the mupirocin peak 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, and measure the peak area responses for all of the peaks. Calculate the percentage of each related compound in the portion of Mupirocin Calcium taken by the formula:

$$(E/200)(W_S/W_U)(r_i/r_S),$$

in which E is the mupirocin equivalent, in µg per mg, of USP Mupirocin Lithium RS; W_S is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard solution;* W_U is the weight, in mg, of Mupirocin Calcium taken to prepare the *Test solution;* r_i is the peak area for any impurity obtained from the *Test solution;* and r_S is the peak area for mupirocin obtained from the *Standard solution:* the area of any peak corresponding to pseudomonic acid D is not greater than 2.5%; the area of any peak, excluding the mupirocin peak and any peak corresponding to pseudomonic acid D, is not greater than 1%; and the sum of the areas of all the peaks, excluding the principal peak, is not greater than 4.5%. Disregard any peak with an area less than 0.05 times the area of the mupirocin peak in the chromatogram obtained from the *Standard solution*.

Assay—

0.1 M Ammonium acetate—Transfer about 7.7 g of ammonium acetate to a 1000-mL volumetric flask, dissolve in about 900 mL of water, adjust with glacial acetic acid to a pH of 5.7, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (68 : 32). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 25 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, dissolve in 5 mL of methanol, dilute with *0.1 M Ammonium acetate* to volume, and mix.

Assay preparation—Transfer about 25 mg of Mupirocin Calcium, accurately weighed, to a 200-mL volumetric flask, dissolve in 5 mL of methanol, dilute with *0.1 M Ammonium acetate* to volume, and mix.

Resolution solution—Adjust 10 mL of the *Standard preparation* with 6 N hydrochloric acid to a pH of 2.0, and allow to stand for 20 hours.

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 7-µm packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* of the second of the two peaks corresponding to hydrolysis products and the peak corresponding to mupirocin is not less than 7.0. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the peak area responses for the major peaks. Calculate the quantity, in µg, of mupirocin ($C_{26}H_{44}O_9$) in each mg of Mupirocin Calcium taken by the formula:

$$E(M_S / M_U)(r_U / r_S),$$

in which E is the designated mupirocin equivalent, in µg, of mupirocin in each mg of the USP Mupirocin Lithium RS; M_S is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard preparation;* M_U is the weight, in mg, of Mupirocin Calcium taken to prepare the *Assay preparation;* and r_U and r_S are the mupirocin peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Mupirocin Cream—See briefing under *Mupirocin Calcium.* In the test for *Related compounds,* typical retention times are about 7.6 minutes for pseudomonic acid F; 12.8 and 13.6 minutes for degradation products; 15.8 and 19.4 minutes for pseudomonic acid D and pseudomonic acid B, respectively; 21.5 minutes for mupirocin; 24.7 and 26.5 minutes for other impurities; and 43.6 and 50.1 minutes for pseudomonic acid C and pseudomonic acid E, respectively. It should be noted that the limits for the test for *Related compounds* apply during the entire shelf-life of the Cream.

(PA7: L. Callahan) RTS—37476-2; 41278-2

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Add the following:

▲Mupirocin Cream

» Mupirocin Cream contains a quantity of Mupirocin Calcium equivalent to not less than 90.0 percent and not more than 120.0 percent of the

labeled amount of mupirocin ($C_{26}H_{44}O_9$). It may contain one or more suitable buffers, dispersants, and preservatives.

Packaging and storage—Preserve in collapsible tubes or well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate that it contains Mupirocin Calcium and its equivalent content of mupirocin.

USP Reference standards ⟨11⟩**—***USP Mupirocin Lithium 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.*

Minimum fill ⟨755⟩**:** meets the requirements.

pH ⟨791⟩**:** between 6.0 and 8.0.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g.

Related compounds—

0.1 M Ammonium acetate, Solution A, Solution B, Mobile phase, pH 6.3 Phosphate buffer, and *Chromatographic system*—Proceed as directed in the *Assay.*

Sodium acetate solution—Add 5.8 mL of glacial acetic acid to 900 mL of water, adjust with sodium hydroxide TS to a pH of 4.0, dilute with water to 1000 mL, and mix.

Tetrahydrofuran solution—Mix 750 mL of tetrahydrofuran and 250 mL of water.

Sodium acetate and tetrahydrofuran solution—Prepare a mixture of *Sodium acetate solution* and *Tetrahydrofuran solution* (50 : 50).

Standard solution—Dissolve an accurately weighed portion of USP Mupirocin Lithium RS in *pH 6.3 Phosphate buffer.* Dilute an accurately measured volume of this solution quantitatively to obtain a solution containing 0.1 mg of mupirocin per mL.

Test stock solution—Transfer an accurately weighed quantity of Cream, equivalent to about 50 mg of mupirocin, to a screw-capped centrifuge tube. Add 5.0 mL of *Tetrahydrofuran solution,* cap, and disperse the Cream by mixing on a vortex mixer and shaking. Add 5.0 mL of *Sodium acetate solution,* cap, and mix. Centrifuge for about 15 minutes. Withdraw the lower layer from the tube, pass it through a filter having a 0.5-µm or finer porosity, and use the filtrate.

Test solution—Transfer 1.0 mL of the *Test stock solution* to a 50-mL volumetric flask, dilute with *Sodium acetate and tetrahydrofuran solution* to volume, mix, and pass through a filter having a 0.5-µm or finer porosity.

pH 4 Acetate buffer—Transfer about 13.6 g of sodium acetate to a 1000-mL volumetric flask, and dissolve in about 900 mL of water. Adjust with glacial acetic acid to a pH of 4.0, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* typical retention times are about 16 minutes for pseudomonic acid D and 21 minutes for mupirocin; the relative retention times are 0.36 for pseudomonic acid F, 0.6 for mupirocin degradation product A, 0.63 for mupirocin degradation product B, 0.74 for pseudomonic acid D, 0.9 for pseudomonic acid B, 1.0 for mupirocin, 1.15 for mupirocin related compound A, 1.23 for mupirocin related compound B, 2.03 for pseudomonic acid C, and 2.15–2.33 for pseudomonic acid E; the resolution, *R,* between pseudomonic acid D and mupirocin is not less than 3; the column efficiency for the mupirocin peak is not less

than 7000 theoretical plates; the tailing factor for the mupirocin peak is not more than 1.75; and the relative standard deviation of the mupirocin peak for replicate injections is not more than 2%.

Procedure—[NOTE—Ensure that buffers, dispersants, or preservatives in the formulation do not interfere with quantification of either impurities or degradation products.] Separately inject equal volumes (about 20 µL) of the *Test stock solution* and the *Test solution* into the chromatograph, and measure the peak responses for all of the peaks that do not correspond to buffers, dispersants, or preservatives. Calculate the percentage of each related compound and degradation product relative to mupirocin in the portion of Cream taken by the formula:

$$2(r_i / r_M),$$

in which r_i is the peak response for each related compound or degradation product obtained from the *Test stock solution;* and r_M is the peak response of the mupirocin peak obtained from the *Test solution:* not more than 3.0% of pseudomonic acid D is found; not more than 8.5% of mupirocin degradation product A is found; not more than 16% of mupirocin degradation product B is found; not more than 1.2% of any other individual impurity or degradation product is found; and not more that 30% of total impurities and degradation products is found.

Assay—

0.1 M Ammonium acetate—Prepare as directed in the *Assay* under *Mupirocin Calcium*.

Solution A—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (75 : 25).

Solution B—Prepare a filtered and degassed mixture of *0.1 M Ammonium acetate* and tetrahydrofuran (70 : 30).

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⟩).

pH 6.3 Phosphate buffer—Dissolve 69 g of monobasic sodium phosphate in 800 mL of water, adust with sodium hydroxide TS to pH 6.3, dilute with water to 1000 mL, and mix.

Standard preparation—Transfer about 21 mg of USP Mupirocin Lithium RS, accurately weighed, to a 200-mL volumetric flask, and dissolve in and dilute with *pH 6.3 Phosphate buffer* to volume.

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 10 mg of mupirocin, to a 100-mL volumetric flask. Add 50 mL of *pH 6.3 Phosphate buffer* and 25 mL of tetrahydrofuran. Insert the stopper into the flask, mix on a vortex mixer, and shake for 1 to 3 minutes. Dilute with *pH 6.3 Phosphate buffer* to volume. Allow to stand until the oil layer separates out, then dilute the aqueous layer with *pH 6.3 Phosphate buffer* to volume. Repeat 2 to 3 times until as much of the oil layer has separated out as possible. After the final dilution, pass the final solution (bottom layer) through a filter having a 0.5-µm or finer porosity.

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 7-µm packing L7. The flow rate is about 1 mL per minute. Maintain the column at a constant temperature up to 35°. The chromatograph is programmed as follows.

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Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–6	100	0	isocratic
6–35	100→0	0→100	linear gradient
35–55	0	100	isocratic
55–55.01	0→100	100→0	immediate
55.01–65	100	0	isocratic

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* typical retention times are about 16 minutes for pseudomonic acid D and 21 minutes for mupirocin; the resolution, *R,* between pseudomonic acid D and mupirocin is not less than 3; the column efficiency for the mupirocin peak is not less than 7000 theoretical plates; the tailing factor for the mupirocin peak is not more than 1.75; and the relative standard deviation of the mupirocin peak for replicate injections is not more than 2%.

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 area responses for the major peaks. Calculate the weight percent of mupirocin in the portion of Cream taken by the formula:

$$0.05E(M_S/M_U)(r_U/r_S),$$

in which M_S is the weight, in mg, of USP Mupirocin Lithium RS taken to prepare the *Standard preparation; E* is the designated mupirocin equivalent, in µg, of mupirocin in each mg of the USP Mupirocin Lithium RS; M_U is the weight, in mg, of Cream taken to prepare the *Assay preparation;* and r_U and r_S are the mupirocin peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Paroxetine Tablets, *USP 28* page 1476. It is proposed to revise *Identification* test *A* to specify the amount of hydrochloric acid used in the preparation of the *Test specimen*. The current procedure uses an inadequate amount of hydrochloric acid in the precipitation step. Also, it is proposed to revise *Identification* test *C* to change angular rotation to specific rotation.

(PA3: R. Ravichandran) RTS—42084-1

Paroxetine Tablets

▲(Title for this new monograph—to become official February 1, 2006)▲*USP28*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Transfer a quantity of finely powdered Tablets, equivalent to about 90 mg of paroxetine, to a suitable flask, add 100 mL of 0.1 N hydrochloric acid, and stir for 1 hour. Transfer the mixture to a separatory funnel, and add ~~ammonium hydroxide until the solution is alkaline to litmus paper~~

▲1.5 mL of ammonium hydroxide to make the solution alkaline.▲*USP29*

Add 100 mL of ethyl ether to the funnel, and shake for 2 minutes. Transfer the organic layer into the necessary number of centrifuge tubes, and centrifuge for 10 minutes. Recombine the clarified extracts, add 1 drop of water and 0.5 mL of ~~0.1 N~~

▲▲*USP29*

hydrochloric acid, stir, and evaporate to dryness under a stream of nitrogen. Dry the residue in an oven at 90° for 1 hour.

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: Place a quantity of finely powdered Tablets, equivalent to about 450 mg of paroxetine, in a stoppered flask. Add 100 mL of alcohol, and shake for 1 hour. Centrifuge about 20 mL of the mixture, and measure the ~~angular~~

▲specific▲*USP29*
rotation of the supernatant at 20° (see *Optical Rotation* ⟨781⟩): the ~~angular~~

▲specific▲*USP29*
rotation is between –75° and –115°.

BRIEFING

Penicillamine Capsules, *USP 28* page 1481 and page 153 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to revise the *Dissolution* test to add an option for carrying out the test in unit samples. The chromatographic procedure for this option was validated using an Atlantis C18 brand of column that contains packing L1. In addition, minor editorial style changes have been made.

(BPC: M. Marques) RTS—42062-1

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

▲▲*USP29*
⟨711⟩—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm.
Time: 30 minutes.

▲PROCEDURE FOR A POOLED SAMPLE—▲*USP29*
Dilute hydrochloric acid—Dilute 37 mL of hydrochloric acid with water to 1 L.
Ammonium sulfamate reagent—Dissolve 250 mg of ammonium sulfamate in 100 mL of *Dilute hydrochloric acid.*
N-(1-Naphthyl)ethylenediamine dihydrochloride reagent—Dissolve 100 mg of *N*-(1-naphthyl)ethylenediamine dihydrochloride in 100 mL of *Dilute hydrochloric acid.*
Sulfanilamide–mercuric chloride reagent—Dissolve 100 mg of sulfanilamide and 100 mg of mercuric chloride in 100 mL of *Dilute hydrochloric acid.*
Sodium nitrite reagent—Dissolve 200 mg of sodium nitrite in 100 mL of dilute sulfuric acid (1 in 50). Prepare fresh.
Standard solution—Dissolve an accurately weighed quantity of USP Penicillamine RS in 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 250 µg per mL.
Procedure—

▲Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the *Test solution.*▲*USP29*
Pipet an aliquot of the ~~filtered test solution,~~ ▲pooled sample▲*USP29* estimated to contain about 278 µg of penicillamine, into a 100-mL volumetric flask. Into a similar flask pipet an equivalent volume of 0.1 N hydrochloric acid to provide a reagent blank, and into a third 100-mL volumetric flask pipet 1 mL of *Standard solution.* Treat each flask as follows. Add by pipet 3 mL of *Sodium nitrite reagent,* and mix by swirling occasionally. After 5 minutes, add 10 mL of *Ammonium sulfamate reagent,* swirl, and allow to stand for an additional 5 minutes. Add 5 mL of *Sulfanilamide–mercuric chloride reagent,* swirl, and immediately add 10 mL of *N-(1-Naphthyl)ethylenediamine dihydrochloride reagent.* Dilute with water to volume, and mix. Determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 540 nm, with a suitable spectrophotometer, against the reagent blank. Calculate the percentage dissolution of the Capsule taken by the formula:

$$90(C/WV)(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Penicillamine RS in the *Standard solution; W* is the labeled quantity, in mg, of penicillamine in the Capsule; V is the volume, in mL, of the aliquot of test solution used; and A_U and A_S are the absorbances of the solutions from the test solution and the *Standard solution,* respectively.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_5H_{11}NO_2S$ is dissolved in 30 minutes:

▲the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q,* is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

PROCEDURE FOR A UNIT SAMPLE —

Buffer solution—Prepare a 50 mM solution of monobasic potassium phosphate buffer, pH 3.0.

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Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (97 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Penicillamine RS in 0.1 N hydrochloric acid having a known concentration corresponding to the content of 1 Capsule dissolved in 900 mL of *Medium*.

Resolution solution—Prepare a solution of USP Penicillamine Disulfide RS in 0.1 N hydrochloric acid having a known concentration of about 0.002 mg per mL.

Test solution—Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. After 30 minutes, withdraw about 10 mL of solution from each vessel, and immediately pass each aliquot through a 0.45-µm polyvinylidene difluoride filter paper. Discard the first 2 mL of filtered solution, and chromatograph the remaining filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equippped with a 210-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. 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 2.0%. Chromatograph the *Resolution solution* and record the peak responses as directed for *Procedure:* the resolution, *R,* between penicillamine and penicillamine disulfide is not less than 2.0.

Procedure—Separately inject equal volumes (about 30 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, in percentage, of $C_5H_{11}NO_2S$ released by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC},$$

in which r_U and r_S are the peak areas obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg, for each Capsule.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_5H_{11}NO_2S$ is dissolved in 30 minutes. ▲*USP29*

BRIEFING

Piperacillin and Tazobactam Injection, page 2000 of *PF* 28(6) [Nov.–Dec. 2001]; **Piperacillin and Tazobactam for Injection,** page 2001 of *PF* 28(6) [Nov.–Dec. 2001]. These proposed new monographs, which previously appeared in *Pharmacopeial Previews,* are now being forwarded to *In-Process Revision*. Editorial style changes have been made.

(PA7a: B. Gilbert) RTS—42216-1

Add the following:

▲Piperacillin and Tazobactam Injection

» Piperacillin and Tazobactam Injection is a sterile solution of Piperacillin Sodium and Tazobactam Sodium that contains the equivalent of not less

than 90.0 percent and not more than 110.0 percent of the labeled amounts of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$), the labeled amounts representing proportions of piperacillin to tazobactam of 8 : 1.

Packaging and storage—Preserve in *Containers for Injections* as described in the *Packaging* section under *Injections* ⟨1⟩. Maintain in the frozen state.

Labeling—Label it to indicate its sodium content. It meets the requirements for *Labeling* under *Injections* ⟨1⟩. The label states that it is to be thawed just prior to use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen.

USP Reference standards ⟨11⟩*—USP Endotoxin RS. USP Piperacillin RS. USP Tazobactam RS.*

Identification—The retention times of the main peaks for piperacillin and tazobactam in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩—It contains not more than 0.08 USP Endotoxin Unit in a portion equivalent to 1 mg of a mixture of piperacillin and tazobactam (0.89 and 0.11 mg, respectively).

pH ⟨791⟩: between 5.0 and 7.0.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase, Standard preparation, and *Chromatographic system—*Proceed as directed in the *Assay* under *Piperacillin and Tazobactam for Injection*.

*Assay preparation—*Allow 1 container of Injection to thaw, and mix. Transfer an accurately measured volume of the Injection, equivalent to about 250 mg of piperacillin and 25 mg of tazobactam, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 25-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 areas for the major peaks. Calculate the quantities, in mg, of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$), respectively, in each mL of Injection taken by the formula:

$$0.25C_S P(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation; P* is the designated potency, in µg, of piperacillin ($C_{23}H_{27}N_5O_7S$) or tazobactam ($C_{10}H_{12}N_4O_5S$) in each mg of the USP Piperacillin RS or the USP Tazobactam RS, as appropriate; and r_U and r_S are the responses of the appropriate analyte peaks obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP29*

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BRIEFING

Piperacillin and Tazobactam for Injection, page 2001 of *PF* 28(6) [Nov.–Dec. 2001]—See briefing under *Piperacillin and Tazobactam Injection*. Also, in this monograph, it is proposed to revise the *Assay* to include the component ratios of the *Mobile phase*.

(PA7a: B. Gilbert) RTS—42156-1

Add the following:

▲Piperacillin and Tazobactam for Injection

» Piperacillin and Tazobactam for Injection contains amounts of Piperacillin Sodium and Tazobactam Sodium equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$), the labeled amounts representing proportions of piperacillin to tazobactam of 8 : 1.

Packaging and storage—Preserve in *Containers for Sterile Solids* as described in the *Packaging* section under *Injections* ⟨1⟩. Store at controlled room temperature.

Labeling—Label it to indicate its sodium content.

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Piperacillin RS. USP Tazobactam RS.*

Identification—The retention times of the main peaks for piperacillin and tazobactam in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.08 USP Endotoxin Unit in a portion equivalent to 1 mg of a mixture of piperacillin and tazobactam (0.89 and 0.11 mg, respectively).

Sterility ⟨71⟩**—**It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩: between 5.0 and 7.0, in a solution containing the equivalent of 40 mg of piperacillin per mL.

Water, *Method I* ⟨921⟩: not more than 2.5%.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a mixture of methanol, water, 0.2 M monobasic sodium phosphate, and 0.4 M tetrabutylammonium hydroxide (510 : 432 : 50 : 8). Adjust with phosphoric acid to a pH of 5.5 ± 0.02. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Prepare a solution of USP Piperacillin RS and USP Tazobactam RS quantitatively in *Mobile phase* to obtain a solution having known concentrations of about 1 mg of USP Piperacillin RS and 0.1 mg of USP Tazobactam RS per mL.

Assay preparation 1 (where it is represented as being in a single-dose container)—Constitute a container of Piperacillin and Tazobactam for Injection with a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Withdraw the total withdrawable contents from the container, using a suitable hypodermic needle and syringe, and dilute quantitatively,

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and stepwise if necessary, with *Mobile phase* to obtain a solution containing the equivalent of about 1 mg of piperacillin and 0.1 mg of tazobactam per mL.

Assay preparation 2 (where the label states the quantities of piperacillin and tazobactam in a given volume of constituted solution)—Constitute a container of Piperacillin and Tazobactam for Injection with a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Dilute an accurately measured volume of the constituted solution quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing the equivalent of about 1 mg of piperacillin and 0.1 mg of tazobactam per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical 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 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 peak area responses for the major peaks. Calculate the quantities, in mg, of piperacillin ($C_{23}H_{27}N_5O_7S$) and tazobactam ($C_{10}H_{12}N_4O_5S$), respectively, withdrawn from the container, or in the volume of constituted solution, taken by the formula:

$$(L/D)(C_S P)(r_U / r_S),$$

in which L is the labeled quantity, in mg, of piperacillin or tazobactam, as appropriate, in the container or in the volume of constituted solution taken; D is the concentration, in mg per mL, of piperacillin or tazobactam in *Assay preparation 1* or *Assay preparation 2,* on the basis of the labeled quantity, in mg, of piperacillin or tazobactam, as appropriate, in the container and the extent of dilution; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation; P* is the designated potency, in µg, of piperacillin ($C_{23}H_{27}N_5O_7S$) or tazobactam ($C_{10}H_{12}N_4O_5S$) in each mg of the USP Piperacillin RS or the USP Tazobactam RS; and r_U and r_S are the responses of the appropriate analyte peaks obtained from *Assay preparation 1* or *Assay preparation 2* and the *Standard preparation,* respectively.▲*USP29*

BRIEFING

Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution, *USP 28* page 1582—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(PA1: K. Russo; D. Bempong) RTS—42196-14

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Assay for anhydrous citric acid—

~~*Cation-exchange column*—Mix 10 g of styrenedivinylbenzene cation-exchange resin with 50 mL of water in a suitable beaker. Allow the resin to settle, and decant the supernatant until a slurry of resin remains. Pour the slurry into a 14-mm × 30-cm glass chromatographic tube (having a sealed-in, coarse-porosity porous glass disk and fitted with a stopcock), and allow to settle as a homogeneous bed. Wash the resin bed with about 100 mL of water, closing the stopcock when the water level is about 2 mm above the resin bed.~~

In-Process Revision

~~*Procedure*—Transfer an accurately measured volume of the stock solution used to prepare *Assay preparation 1* in the *Assay for potassium bicarbonate and sodium bicarbonate,* equivalent to about 40 mg of anhydrous citric acid, carefully onto the top of the resin bed in the *Cation exchange column*. Place a 250-mL conical flask below the column, open the stopcock, and allow to flow until the solution has entered the resin bed. Elute the column with 60 mL of water at a flow rate of about 5 mL per minute, collecting about 65 mL of the eluate in a suitable flask. Boil the eluate for 1 minute, cool, add 5 drops of phenolphthalein TS, swirl the flask, and titrate with 0.02 N sodium hydroxide VS to a pink endpoint. Each mL of 0.02 N sodium hydroxide is equivalent to 1.281 mg of $C_6H_8O_7$.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of the stock solution used to prepare *Assay preparation 1* in the *Assay for potassium bicarbonate and sodium bicarbonate,* equivalent to about 40 mg of anhydrous citric acid into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the portion of Tablets taken by the formula:

$$0.001(192.12/189.10)C_S D(r_U / r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.▲*USP29*

(Official January 1, 2009)

BRIEFING

Potassium Bromide; Sodium Bromide. Because there are no existing *USP* monographs for these articles, new monographs are being proposed. Potassium Bromide and Sodium Bromide are used in veterinary medicine as components of compounded preparations to treat refractory epilepsy in dogs and cats. These drug substance monographs are being proposed as a prelude to the publication of monographs for the compounded formulations.

(VET: I. DeVeau) RTS—41869-1

Add the following:

▲Potassium Bromide

Potassium bromide 119.0 [*7758-02-3*].

» Potassium Bromide contains not less than 98.0 percent and not more than 100.5 percent of KBr, calculated on the dried basis. It contains no added substances.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

Appearance of solution: clear and colorless.

Test solution—Dissolve 10.0 g in carbon dioxide-free water, and dilute with the same solvent to 100 mL.

Identification—

A: A solution containing 4.5 mg of potassium bromide responds to the test for *Bromide* ⟨191⟩.

B: Responds to the test for *Potassium* ⟨191⟩.

Acidity or alkalinity—To 10 mL of the solution prepared for the test for *Appearance of solution,* add 0.1 mL of bromothymol blue TS: not more than 0.5 mL of 0.01 N hydrochloric acid or 0.01 N sodium hydroxide is required to change the color of this solution.

In-Process Revision

Loss on drying ⟨731⟩—Dry it at 100° to 105° for 3 hours: it loses not more than 1.0% of its weight.

Bromates—

Starch–mercuric iodide solution—Triturate 1.0 g of soluble starch with 5 mL of water and pour the mixture into 100 mL of boiling water, containing 10 mg of mercuric iodide.

Procedure—To 10 mL of the solution prepared for the test for *Appearance of solution* add 1 mL of *Starch–mercuric iodide solution,* 0.1 mL of a 100 g per L solution of potassium iodide, and 0.25 mL of 0.5 M sulfuric acid. Allow to stand protected from light for 5 minutes. No blue or violet color develops.

Limit of chlorine: not more than 0.6 percent.

Nitric acid solution and *Ferric ammonium sulfate solution*—Proceed as directed in the *Assay.*

Procedure—Dissolve 1.000 g of Potassium Bromide in 20 mL of *Nitric acid solution* in a conical flask, add and mix 5 mL of 30 percent hydrogen peroxide, and heat in a water bath until the solution is colorless. Rinse the sides of the flask with a small quantity of water, and heat in a water bath for 15 minutes. Allow to cool, dilute with water to 50 mL, and add 5.0 mL of silver nitrate VS and 1 mL of dibutyl phthalate. Mix, and back titrate the excess silver nitrate with ammonium thiocyanate VS (see *Titrimetry* ⟨541⟩), using 5 mL of *Ferric ammonium sulfate solution* as the indicator. Perform a blank titration. Not more than 1.7 mL of silver nitrate VS is used.

Iodides—To 5 mL of the solution prepared for the test for *Appearance of solution* add 0.15 mL of a 10.5 g per 100 mL ferric chloride solution, and 2 mL of dichloromethane. Shake, and allow to separate. The lower layer is colorless.

Sulfates ⟨221⟩—A 2.0-g portion shows no more sulfate than corresponds to 0.2 mL of 0.020 N sulfuric acid (0.01%).

Limit of iron: not more than 20 ppm.

Citric acid solution—Prepare a 200 g citric acid per mL solution.

Iron standard solution—Transfer 0.863 g of ferric ammonium sulfate to a 500-mL volumetric flask, and dissolve in 25 mL of dilute sulfuric acid. Dilute with water to volume. Transfer 1.0 mL of the resulting solution to a 10-mL volumetric flask, and dilute with water to volume. Transfer 2.5 mL of this resulting solution to a 50-mL volumetric flask, and dilute with water to volume. [NOTE—Prepare immediately before use.]

Test solution—Transfer 5 mL of the solution prepared for the test for *Appearance of solution* to a 10-mL volumetric flask, and dilute with water to volume.

Procedure—To 10 mL each of the *Iron standard solution* and the *Test solution* add 2.0 mL of the *Citric acid solution* and 0.1 mL of thioglycolic acid. Make alkaline to litmus with ammonia water, and dilute with water to 20 mL. After 5 minutes, any pink color in the *Test solution* is not more intense than that in the *Iron standard solution*.

Magnesium and alkaline-earth metals—To 200 mL of water add 0.1 g of hydroxylamine hydrochloride, 10 mL of pH 10.0 ammonia–ammonium chloride buffer (prepared by dissolving 5.4 g of ammonium chloride in 20 mL of water, adding 20 mL of ammonium hydroxide and diluting to 100 mL), 1 mL of 0.1 M zinc sulfate, and about 0.2 g of eriochrome black T trituration. Heat to about 40°. Titrate this solution (see *Titrimetry* ⟨541⟩) with 0.01 M edetate disodium VS until the violet color changes to deep blue. To this solution add 10.0 g of Potassium Bromide dissolved in 100 mL of water. If the color changes to violet, titrate the solution with 0.01 M edetate disodium VS to a deep blue endpoint. The volume of 0.01 M edetate disodium consumed in the second titration does not exceed 5.0 mL (0.02%, calculated as Ca).

Heavy metals, *Method I* ⟨231⟩**:** not more than 10 ppm.

In-Process Revision

Assay—

Nitric acid solution—Dilute 14 mL of nitric acid with water to 100 mL.

Ferric ammonium sulfate solution—Transfer 10 g of ferric ammonium sulfate to a 100-mL volumetric flask. Dissolve in and dilute with water to volume.

Procedure—Dissolve 2.000 g of Potassium Bromide in water, and dilute with water to 100.0 mL. To 10.0 mL of the solution add 50 mL of water, 5 mL of *Nitric acid solution,* 25.0 mL of silver nitrate VS, and 2 mL of dibutyl phthalate. Mix, and back titrate the excess silver nitrate with ammonium thiocyanate VS (see *Titrimetry* ⟨541⟩), using 2 mL of *Ferric ammonium sulfate solution* as the indicator, shaking vigorously towards the endpoint. Each mL of 0.1 M silver nitrate is equivalent to 11.90 mg of KBr. Calculate the percent content of Potassium Bromide, corrected for the chloride content, by the formula:

$$a - 3.357b,$$

in which a is the percent content of KBr and KCl obtained, calculated as KBr; and b is the percent content of chlorides.▲*USP29*

BRIEFING

Potassium Citrate Extended-Release Tablets, *USP 28* page 1590—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(DSN: L. Evans; D. Bempong) RTS—42196-15

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Assay—

~~*Standard preparation*—Dissolve a suitable quantity of citric acid, previously dried at 90° for 3 hours and accurately weighed, in water to obtain a solution having a known concentration of about 1.0 mg of anhydrous citric acid per mL.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.▲*USP29*

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of potassium citrate, to a 1000-mL volumetric flask, add about 300 mL of hot water, and shake by mechanical means for 15 minutes. Allow to cool, dilute with water to volume, and mix. Filter, discarding the first 30 mL of the filtrate. ~~Transfer 20.0 mL of the clear filtrate to a 25-mL volumetric flask, dilute with water to volume, and mix.~~

▲Transfer an aliquot of the clear filtrate into a suitable volumetric flask, and dilute with water and freshly prepared sodium hydroxide solution to obtain a solution containing about 20 µg per mL citrate in 1 mM sodium hydroxide.▲*USP29*

[NOTE—Reserve the remaining filtrate for the test for *Potassium content.*]

~~*Standard curve*—Pipet aliquots of 8, 9, 10, 11, and 12 mL, respectively, of the *Standard preparation* into separate 100-mL volumetric flasks, dilute with water to volume, and mix. These solutions contain about 0.08, 0.09, 0.10, 0.11, and 0.12 mg of anhydrous citric acid per mL, respectively. Continue as directed for *Procedure*. Plot the resultant absorbances versus the respective concentrations, in mg per mL, of the standard solutions.~~

~~*Procedure*—Pipet 1 mL of the *Assay preparation* into a suitable test tube. To a second test tube add 1.0 mL of water to serve as a reference blank. To each tube add 1.3 mL of pyridine, and mix by swirling. To one tube at a time add 5.7 mL of acetic anhydride, and mix, using a rotary vortex stirrer. Immediately place in a water bath maintained at 31 ± 1.0°, and allow the color to develop for 33 ± 1 minutes. Determine the absorbance against the reference blank in 2.5-cm cells at 425 nm, taking care to measure the absorbance of each solution at the same elapsed time from mixing. Calculate the quantity, in mg, of $C_6H_8K_2O_7$ in the portion of Tablets taken by the formula:~~

~~$$(306.40/192.13)(1250C),$$~~

~~in which 306.40 and 192.13 are the molecular weights of anhydrous potassium citrate and anhydrous citric acid, respectively, and C is the concentration, in mg per mL, of anhydrous citric acid read from the *Standard curve*.~~

In-Process Revision

▲*Procedure*—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the quantity, in mg, of potassium citrate ($C_6H_5K_3O_7$) in the portion of Tablets taken by the formula:

$$0.001(306.39/189.10)C_S D(r_U / r_S),$$

in which 306.39 is the molecular weight of potassium citrate; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.▲*USP29*

(Official January 1, 2009)

BRIEFING

Potassium Citrate and Citric Acid Oral Solution, *USP 28* page 1590—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(PA1: K. Russo; D. Bempong) RTS—42196-13

In-Process Revision

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Assay for citrate—

~~*Cation-exchange column*—Mix 10 g of styrene-divinylbenzene cation-exchange resin with 50 mL of water in a suitable beaker. Allow the resin to settle, and decant the supernatant until a slurry of resin remains. Pour the slurry into a 15 mm × 30 cm glass chromatographic tube (having a sealed-in, coarse-porosity fritted disk and fitted with a stopcock), and allow to settle as a homogeneous bed. Wash the resin bed with about 100 mL of water, closing the stopcock when the water level is about 2 mm above the resin bed.~~

~~*Procedure*—Pipet 15 mL of Oral Solution into a 250-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution carefully onto the top of the resin bed in the *Cation-exchange column*. Place a 250-mL conical flask below the column, open the stopcock, and allow to flow until the solution has entered the resin bed. Elute the column with 60 mL of water at a flow rate of about 5 mL per minute, collecting about 65 mL of the eluate. Add 5 drops of phenolphthalein TS to the eluate, swirl the flask, and titrate with 0.02 N sodium hydroxide VS. Record the buret reading, and calculate the volume *(B)* of 0.02 N sodium hydroxide consumed. Each mL of the difference between the volume *(B)* and the volume *(A)* of 0.02 N sodium hydroxide consumed in the *Assay for citric acid* is equivalent to 1.261 mg of $C_6H_8O_7$.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Pipet 15 mL of Oral Solution into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the concentration, in mg per mL, of citrate ($C_6H_5O_7^{-3}$) in the Oral Solution taken by the formula:

$$0.001C_S(D / V)(r_U / r_S) - A(189.10 / 210.14),$$

in which C_S is the concentration, in µg per mL, of citrate in *Standard preparation 1; D* is the dilution factor; *V* is the volume of Oral Solution used in the preparation of the *Assay preparation;* r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); 210.14 is the molecular weight of citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$); and *A* is the concentration of citric acid monohydrate, in mg per mL, determined in the *Assay for citric acid.*▲*USP29*

(Official January 1, 2009)

BRIEFING

Oral Rehydration Salts, *USP 28* page 1708 and page 1646 of *PF* 30(5) [Sept.–Oct. 2004]—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(PA1: K. Russo; D. Bempong) RTS—42196-12

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.* ▲*USP29*

(Official January 1, 2009)

Change to read:

Assay for dextrose—Transfer the contents of 1 or more unit-dose containers of Oral Rehydration Salts, or an accurately weighed portion of the contents of 1 multiple-unit container, equivalent to about 20 g of dextrose, to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 50.0 mL of this stock solution to a 100-mL volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. [NOTE—Reserve the remaining stock solution for the *Assay for sodium and potassium,* the *Assay for chloride,* the *Assay for bicarbonate,* and the *Assay for citrate.*] Determine the angular rotation in a suitable polarimeter tube ~~at 25° (see *Optical Rotation* ⟨781⟩). Calculate the quantity, in g, of anhydrous dextrose ($C_6H_{12}O_6$) in the unit-dose container or containers taken or in the portion of powder taken from the multiple-unit container, by the formula:~~

~~$(200/52.7)(a/l)$,~~

~~in which 52.7 is the specific rotation of anhydrous dextrose, a is the corrected observed rotation, in degrees, and l is the length, in dm, of the polarimeter tube. Where the Oral Rehydration Salts is labeled to contain Dextrose Monohydrate, calculate the quantity of dextrose monohydrate ($C_6H_{12}O_6 \cdot H_2O$) by the same formula, substituting the figure 47.9, the specific rotation of dextrose monohydrate, in place of 52.7.~~

■(see *Optical Rotation* ⟨781⟩). Where the Oral Rehydration Salts is labeled to contain anhydrous dextrose, calculate the percentage (g per 100 mL) of $C_6H_{12}O_6$ in the portion of Oral Rehydration Salts taken by the formula:

$$(100/52.9)AR,$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; A is 100 mm divided by the length of the polarimeter tube, in mm; and R is the observed rotation, in degrees. Where the Oral Rehydration Salts is labeled to contain dextrose monohydrate, calculate the percentage (g per 100 mL) of $C_6H_{12}O_6 \cdot H_2O$ in the portion of Oral Rehydration Salts taken by the formula:

$$(100/52.9)(198.17/180.16)AR,$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; A is 100 mm divided by the length of the polarimeter tube, in mm; and R is the observed rotation, in degrees. ■2S *(USP28)*

Change to read:

Assay for citrate *(if present)*—

~~*Mobile phase*—Dissolve 20 g of ammonium sulfate in a mixture of water and acetonitrile (980 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of sodium citrate, previously dried at 180° for 18 hours, in water to obtain a solution having a known concentration of about 2.5 mg of anhydrous sodium citrate per mL.~~

~~*Assay preparation*—Transfer an accurately measured volume of the stock solution remaining from the *Assay for dextrose*, equivalent to about 180 mg of citrate ($C_6H_5O_7^{-3}$), to a 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.8-mm × 20-cm column that contains packing L8. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak response as directed for *Procedure*: the retention time for the citrate peak is about 3 minutes, 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%. [NOTE—The column may be equilibrated before use by making a series of injections of the *Standard preparation* over a period of several hours. If the tailing factor is greater than 2, the equilibration may be facilitated by adding 1 g of sodium citrate to each 1000 mL of the *Mobile phase* and pumping this solution through the column at about 0.5 mL per minute for several hours. The column must then be washed with *Mobile phase* for a few minutes before use.]~~

~~*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 $C_6H_5O_7^{-3}$ in the unit-dose container or containers taken or in the portion of powder taken from the multiple-unit container by the following formula:~~

~~$(189.12/258.07)(10{,}000C/v)(r_u/r_s)$,~~

~~in which 189.12 and 258.07 are the molecular weights of citrate ($C_6H_5O_7^{-3}$) and anhydrous sodium citrate, respectively, C is the concentration, in mg per mL, of anhydrous sodium citrate in the~~

In-Process Revision

~~*Standard preparation,* r_U is the volume, in mL, of the stock solution taken to prepare the *Standard preparation,* and r_U and r_S are the citrate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of the stock solution remaining from the *Assay for dextrose*, equivalent to about 180 mg of citrate ($C_6H_5O_7^{-3}$), to a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩. Calculate the quantity, in mg, of citrate ($C_6H_5O_7^{-3}$) in the portion of Oral Rehydration Salts taken by the formula:

$$0.001 C_S D(r_U / r_S),$$

in which C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.▲*USP29*

(Official January 1, 2009)

BRIEFING

Sodium Bromide—See briefing under *Potassium Bromide.*

(VET: I. DeVeau) RTS—41869-2

In-Process Revision

Add the following:

▲Sodium Bromide

Sodium bromide 102.89 [*7647-15-6*].

» Sodium Bromide contains not less than 98.0 percent and not more than 100.5 percent of NaBr, calculated on the dried basis. It contains no added substances.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

Appearance of solution: clear and colorless.

Test solution—Dissolve 10.0 g in carbon dioxide-free water, and dilute with the same solvent to 100 mL.

Identification—

A: A solution containing 4.0 mg of sodium bromide responds to the test for *Bromide* ⟨191⟩.

B: Responds to the test for *Sodium* ⟨191⟩.

Acidity or alkalinity—To 10 mL of the solution prepared for the test for *Appearance of solution,* add 0.1 mL of bromothymol blue TS: not more than 0.5 mL of 0.01 N hydrochloric acid or 0.01 N sodium hydroxide is required to change the color of this solution.

Loss on drying ⟨731⟩**—**Dry it at 100° to 105° for 3 hours: it loses not more than 3.0% of its weight.

Bromates—

Starch–mercuric iodide solution—Triturate 1.0 g of soluble starch with 5 mL of water, and pour the mixture into 100 mL of boiling water containing 10 mg of mercuric iodide.

Procedure—To 10 mL of the solution prepared for the test for *Appearance of solution* add 1 mL of *Starch–mercuric iodide solution,* 0.1 mL of a 100 g per L solution of potassium iodide, and 0.25 mL of 0.5 M sulfuric acid. Allow to stand protected from light for 5 minutes. No blue or violet color develops.

Limit of chlorine: not more than 0.6%.

Nitric acid solution and *Ferric ammonium sulfate solution*—Proceed as directed in the *Assay.*

Procedure—Dissolve 1.000 g Sodium Bromide in 20 mL of *Nitric acid solution* in a conical flask, add and mix 5 mL of 30 percent hydrogen peroxide, and heat in a water bath until the solution is colorless. Rinse the sides of the flask with a small quantity of water, and heat in a water bath for 15 minutes. Allow to cool, dilute with water to 50 mL, and add 5.0 mL of silver nitrate VS and 1 mL of dibutyl phthalate. Mix, and back titrate the excess silver nitrate with ammonium thiocyanate VS (see *Titrimetry* ⟨541⟩), using 5 mL of *Ferric ammonium sulfate solution* as the indicator. Perform a blank titration. Not more than 1.7 mL of silver nitrate VS is used.

Iodides—To 5 mL of the solution prepared for the test for *Appearance of solution* add 0.15 mL of a 10.5 g per 100 mL ferric chloride solution, and 2 mL of dichloromethane. Shake, and allow to separate. The lower layer is colorless.

Sulfates ⟨221⟩**—**A 2.0-g portion shows no more sulfate than corresponds to 0.2 mL of 0.020 N sulfuric acid (0.01%).

Limit of iron: not more than 20 ppm.

Citric acid solution—Prepare a 200 g citric acid per mL solution.

Iron standard solution—Transfer 0.863 g of ferric ammonium sulfate to a 500-mL volumetric flask, and dissolve in 25 mL of dilute sulfuric acid. Dilute with water to volume. Transfer 1.0 mL of the resulting solution to a 10-mL volumetric flask, and dilute with water to volume. Transfer 2.5 mL of this resulting solution a 50-mL volumetric flask, and dilute with water to volume. [NOTE—Prepare immediately before use.]

Test solution—Transfer 5 mL of the solution prepared for the test for *Appearance of solution* to a 10-mL volumetric flask, and dilute with water to volume.

Procedure—To 10 mL each of the *Iron standard solution* and the *Test solution* add 2.0 mL of the *Citric acid solution* and 0.1 ml of thioglycolic acid. Make alkaline to litmus with ammonia water, and dilute with water to 20 mL. After 5 minutes, any pink color in the *Test solution* is not more intense than that in the *Iron standard solution*.

Magnesium and alkaline-earth metals—To 200 mL of water add 0.1 g of hydroxylamine hydrochloride, 10 mL of pH 10.0 ammonia–ammonium chloride buffer (prepared by dissolving 5.4 g of ammonium chloride in 20 mL of water, adding 20 mL of ammonium hydroxide, and diluting to 100 mL), 1 mL of 0.1 M zinc sulfate, and about 0.2 g of eriochrome black T trituration. Heat to about 40°. Titrate this solution (see *Titrimetry* ⟨541⟩) with 0.01 M edetate disodium VS until the violet color changes to deep blue. To this solution add 10.0 g of Sodium Bromide dissolved in 100 mL of water. If the color changes to violet, titrate the solution with 0.01 M edetate disodium VS to a deep blue endpoint. The volume of 0.01 M edetate disodium consumed in the second titration does not exceed 5.0 mL (0.02%, calculated as Ca).

Heavy metals, *Method I* ⟨231⟩**:** not more than 10 ppm.

Assay—

Nitric acid solution—Dilute 14 mL of nitric acid with water to 100 mL.

Ferric ammonium sulfate solution—Transfer 10 g of ferric ammonium sulfate to a 100-mL volumetric flask. Dissolve in and dilute with water to volume.

Procedure—Dissolve 2.000 g of Sodium Bromide in water and dilute to 100.0 mL. To 10.0 mL of the solution add 50 mL of water, 5 mL of *Nitric acid solution,* 25.0 mL of silver nitrate VS, and 2 mL of dibutyl phthalate. Mix, and back titrate the excess silver nitrate with ammonium thiocyanate VS (see *Titrimetry* ⟨541⟩), using 2 mL of *Ferric ammonium sulfate solution* as the indicator, shaking vigorously

towards the endpoint. Each mL of 0.1 M silver nitrate is equivalent to 10.29 mg of KBr. Calculate the percent content of Sodium Bromide, corrected for the chloride content, by the formula:

$$a - 2.902b,$$

in which a is the percent content of NaBr and NaCl obtained, calculated as NaBr; and b is the percent content of chlorides. ▲*USP29*

BRIEFING

Technetium ^{99m}Tc Fanolesomab Injection. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(PA5: A.Wilk) RTS—42148-1

Add the following:

▲Technetium ^{99m}Tc Fanolesomab Injection

» Technetium ^{99m}Tc Fanolesomab Injection is a sterile, nonpyrogenic preparation of anti-CD15 antibody, a partially reduced murine IgM monoclonal antibody that is labeled with ^{99m}Tc and is suitable for intravenous administration. It may contain reducing agents, buffers, and stabilizers. It contains no antimicrobial agents. Other chemical forms of radioactivity do not exceed 10 percent of the total radioactivity. *[Caution—Components of the commercial kit that are used to prepare the Injection are not to be administered directly to the patient.]*

Packaging and storage—Preserve in single-dose containers.

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under *Injections* ⟨1⟩: the time and date of calibration; the amount of ^{99m}Tc as labeled fanolesomab expressed in MBq (or mCi) per mL at the time of calibration; the expiration date and time; the storage temperature; and the statement "Caution—Radioactive Material". The labeling indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours and that, in making dosage calculations, correction is to be made for radioactive decay. The labeling also states that the Injection is to be used within 6 hours following constitution.

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

Bacterial endotoxins ⟨85⟩**:** not more than 0.1 Endotoxin Unit per µg of fanolesomeb in the prepared Injection.

pH ⟨791⟩**:** between 5.8 and 6.6.

Particulate matter ⟨788⟩—It meets the requirements for particulate matter specified for small-volume injections.

Radiochemical purity—

SYSTEM 1: *(free pertechnetate ^{99m}Tc)*

Adsorbent: instant thin-layer chromatography (ITLC) strips[1], heat-treated at 110° for 30 minutes.

Test solution—Use the Injection.

Application volume—Apply 3 µL of the *Test solution* to the origin.

[1] ITLC strips for free pertechnetate 99mTc may be obtained from Sunset Scientific Strips LLC (product number 10503), P.O. Box: 3895, Albuquerque, NM 87190-3895.

In-Process Revision

Developing solvent system: methyl ethyl ketone (MEK).

Procedure—Apply the *Test solution* about 2 cm from the bottom of the *Adsorbent* strip. Immediately develop by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm from the origin. The radiochemical impurity, free pertechnetate ^{99m}Tc, migrates to the top section, while colloidal ^{99m}Tc and technetium ^{99m}Tc fanolesomab remains near the origin on the bottom section. Allow the chromatogram to air-dry. Determine the distribution of radioactivity on the chromatogram by cutting the developed strip at 4 cm from the bottom and then separately measuring and recording the net radioactivity in the top and bottom sections using a suitable radiation detector. Calculate the percentage of free pertechnetate ^{99m}Tc in the Injection by the formula:

$$100\,A_T / (A_T + A_B),$$

in which A_T is the radioactivity measured on the top section; and A_B is the radioactivity measured on the bottom section.

SYSTEM 2: *(colloidal ^{99m}Tc)*

Adsorbent—Use affinity thin-layer chromatography (ATLC) strips[2] that have been soaked in a solution of 50% newborn calf serum (NBCS)[3] in water and allowed to air-dry overnight.

Test solution—Use the Injection.

Developing solvent system: 4% alcohol in 0.3 M sodium chloride.

Application volume—Prespot the point of origin with 3 µL of *Developing solvent system* followed immediately by 3 µL of the *Test solution*.

Procedure—Apply the *Test solution* about 2 cm from the bottom of the *Adsorbent* strip. Immediately develop the strip by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm above the origin. The radiochemical impurity, colloidal ^{99m}Tc, will remain at the origin, while free pertechnetate ^{99m}Tc and technetium ^{99m}Tc fanolesomab migrate close to the solvent front. Remove the strip, and allow to air-dry. Cut the strip 4 cm from the bottom, and separately measure and record the background-corrected radioactivity found in the top and bottom sections, using a suitable radiation detector. Calculate the percentage of colloidal ^{99m}Tc by the formula:

$$100\,A_B / (A_B + A_T),$$

in which A_B is the radioactivity measured in the bottom section; and A_T is the radioactivity measured in the top section. The sum of the result for free pertechnetate ^{99m}Tc in *System 1* and for colloidal ^{99m}Tc measured in *System 2* is not more than 10%.

Immunoreactivity—

Adsorbent—Use affinity thin-layer chromatography (ATLC) strips[2] that have been soaked in a solution of 50% newborn calf serum (NBCS)[3] in water and allowed to air-dry overnight.

Diluent—Prepare a mixture of NBCS and pH 7.4 phosphate-buffered saline (PBS) (1 : 1).

Test solution—Use the Injection diluted with *Diluent* (1 in 4).

[2] ATLC strips for colloidal 99mTc may be obtained from Sunset Scientific Strips LLC (product number 10506), P.O. Box: 3895, Albuquerque, NM 87190-3895.

[3] NBCS (heat inactivated) may be obtained from GIBCO/Invitrogen Corp. (catalog number 26010-074), 1600 Faraday Avenue, P.O. Box 6482, Carlsbad, CA 92008

REFERENCE MATERIALS—

Positive control: CD15 positive HL-60 (ATCC No. CCL240) formalin fixed-cell suspension (12×10^6 cells per mL).

Negative control: CD15 negative Raji (ATCC No. CCL86) formalin fixed-cell suspension (12×10^6 cells per mL).

Application volume—Thaw, and mix the HL-60 and Raji cell stock suspensions. Dispense 90-µL aliquots into individual incubation tubes. Add 3 µL of the *Test solution* to each incubation tube, and mix on a vortex mixer for 5 seconds. Incubate for 30 minutes with gentle rocking at $37 \pm 2°$.

Developing solvent system—Prepare a solution containing 0.05% sodium azide and 4% alcohol in 10 mM phosphate-buffered saline, pH 7.4 (PBS). Pass through a filter having a porosity of 0.22 µm.

Procedure—Mix each incubation tube on a vortex mixer. Immediately remove, and apply 10 µL of sample to the origin of the *Adsorbent* ATLC strip (2 cm from bottom). Allow the sample to adsorb onto the strip, and immediately develop the strip by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm from the origin. Remove the strips, and allow to air-dry. Cut both strips 4 cm above the origin. Separately measure and record the background-corrected radioactivity found on the top and bottom sections of each strip, using a suitable radiation detector. Immunoreactive technetium ^{99m}Tc fanolesomab, bound to the HL-60 cells, remains at the origin, while nonbound forms of ^{99m}Tc migrate away from the origin. Nonspecific binding is measured using the Raji negative control cells. Calculate the specific immunoreactive binding by the formula:

$$[100A_{B(HL\text{-}60)}/(A_{B(HL\text{-}60)} + A_{T(HL\text{-}60)})] - [100A_{B(Raji)}/(A_{B(Raji)} + A_{T(Raji)})],$$

in which $A_{B(HL\text{-}60)}$ and $A_{B(Raji)}$ are the radioactivity of the HL-60 positive control cells and Raji negative control cells, respectively, measured on the bottom section of each strip; and $A_{T(HL\text{-}60)}$ and $A_{T(Raji)}$ are the radioactivity of the HL-60 positive control cells and Raji negative control cells measured on the top section of each strip. A minimum specific immunoreactive binding of 40% is required for the CD15-positive HL-60 cells.

Other requirements—It meets the requirements for *Radionuclide identification* and *Radionuclidic purity* under *Sodium Pertechnetate Tc 99m Injection*. It also meets the requirements under *Injections* ⟨1⟩, except that it may be distributed or dispensed prior to completion of the test for *Sterility,* the latter test being started on the date of manufacture.

Assay for radioactivity ⟨821⟩**—**Using a suitable counting assembly (see *Selection of a Counting Assembly*), determine the radioactivity, in MBq (or mCi) per mL, of Injection by use of a calibrated system.▲*USP29*

BRIEFING

Terbutaline Sulfate Inhalation Aerosol, *USP 28* page 1869. It is proposed to revise the *USP Reference standards* section and the *Assay* to reflect the availability of USP Terbutaline Related Compound A RS (3,5-dihydroxy-ω-*tert*-butylaminoacetophenone sulfate). In addition, minor editorial style changes have been made. Please note that the revisions proposed for this monograph in *PF* 26(3) [May–June 2000] have been canceled.

(AER: K. Zaidi) RTS—42069-1

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩—*USP Terbutaline Sulfate RS.*

▲*USP Terbutaline Related Compound A RS.*▲*USP29*

Change to read:

Assay—

Mobile phase—Prepare a solution containing 750 mL of water, 140 mL of methanol, 110 mL of tetrahydrofuran, and 1.08 g of sodium 1-octanesulfonate. Filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve suitable quantities of USP Terbutaline Sulfate RS and ~~3,5-dihydroxy-ω-*tert*-butylaminoacetophenone sulfate~~

▲USP Terbutaline Related Compound A RS▲*USP29*
in water to obtain a solution containing about 50 µg per mL and 20 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Terbutaline Sulfate RS in water to obtain a solution having a known concentration of about 0.3 mg per mL.

Assay preparation—Accurately weigh not fewer than three containers, and separately perform the following procedure for each of the units. Chill in a dry ice–acetone mixture to about –75° for 15 to 20 minutes. Quickly and carefully remove the top of the container with a tube cutter. Allow the propellants to evaporate at room temperature for 10 to 15 minutes. [NOTE—Avoid complete evaporation of the propellants.] Quantitatively transfer the suspension to a 500-mL separatory funnel with the aid of chloroform. Wash all parts of the container alternately with several small portions of chloroform followed by small portions of 0.01 N sulfuric acid. Transfer the washings to the separatory funnel, and adjust the phase volumes to about 100 mL each with chloroform and 0.01 N sulfuric acid, respectively. Dry the container and all of its parts at 105° for 1 hour. Cool to room temperature, and weigh. Shake the separatory funnel for 1 minute, allow the phases to separate, and discard the chloroform layer. Pass the acidic aqueous phase through filter paper into a 250-mL volumetric flask. Wash the separatory funnel with two 10-mL portions of water, and transfer the washings to the volumetric flask. Dilute with water to volume, mix, and filter, discarding the first 2 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector, a 0.5-µm precolumn, and a 6.2-mm × 8-cm column that contains 3-µm packing L7. The column temperature is maintained at 40°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about ~~0.83 and 1.0~~

▲1.0 and 0.83▲*USP29*
for terbutaline and ~~3,5-dihydroxy-ω-*tert*-butylaminoacetophenone~~

▲terbutaline related compound A,▲*USP29*
respectively; and the resolution, *R,* between terbutaline sulfate and ~~3,5-dihydroxy-ω-*tert*-butylaminoacetophenone~~

▲terbutaline related compound A▲*USP29*
is not less than 1.6. 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 responses for the major peaks. Calculate the quantity, in mg, of terbutaline sulfate $[(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4]$ in each container taken by the formula:

$$250C(r_U/r_S),$$

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

BRIEFING

Tetracaine Hydrochloride, *USP 28* page 1881. It is proposed to revise *Identification* test *A* to clarify the preparation of the *Buffer No. 6, 10 percent, pH 6.0.* This buffer is prepared according to the instructions in *Phosphate Buffers and Other Solutions* under *Antibiotics—Microbial Assays* ⟨81⟩. For the purposes of this *Identification* test, it is not necessary to sterilize the buffer.

(PA1: K. Russo) RTS—42212-1

Change to read:

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Solution—~~Prepare the test solution as follows. Dissolve about 50 mg, accurately weighed, in water to make 250.0 mL. Pipet 5 mL of this solution into a 100-mL volumetric flask, add 2 mL of *Buffer No. 6,* 10 percent, pH 6.0 (see *Phosphate Buffers* ⟨81⟩), then dilute with water to volume, and mix.~~

▲Prepare the test solution as follows. Dissolve about 50 mg, accurately weighed, in water to make 250.0 mL. Pipet 5 mL of this solution into a 100-mL volumetric flask, add 2 mL of *Buffer No. 6, 10 percent, pH 6.0* (see *Antibiotics—Microbial Assays* ⟨81⟩), then dilute with water to volume, and mix. For the purposes of this test, *Buffer No. 6, 10 percent, pH 6.0* does not have to be sterilized.▲*USP29*

Absorptivities at 310 nm, calculated on the anhydrous basis, do not differ by more than 2.0%.

B: Dissolve 100 mg in 10 mL of water, and add 1 mL of potassium thiocyanate solution (1 in 4): a crystalline precipitate is formed. Recrystallize the precipitate from water, and dry at 80° for 2 hours: it melts between 130° and 132°.

C: A solution of 100 mg in 5 mL of water meets the requirements of the tests for *Chloride* ⟨191⟩.

In-Process Revision

BRIEFING

Thalidomide, *USP 28* page 1893. On the basis of comments received, it is proposed to revise the calculation in the test for *Chromatographic purity* to include a factor to convert the value obtained to percent.

(PA6: L. Evans) RTS—42247-1

Change to read:

Chromatographic purity—

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (95 : 5 : 0.1).

Solution B—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (85 : 15 : 0.1).

Diluent—Prepare a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 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⟩).

Phthalic acid stock solution—Transfer about 100 mg of phthalic acid to a 100-mL volumetric flask, dissolve in a mixture of acetonitrile and water (80 : 5), and dilute with acetonitrile to volume. Mix, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.1 mg per mL.

Standard stock solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Thalidomide RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Pipet 2.0 mL of the *Standard stock solution* and 2.0 mL of the *Phthalic acid stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.0002 mg of phthalic acid per mL.

Test solution—Transfer about 100 mg of Thalidomide, accurately weighed, to a 50-mL volumetric flask, and dissolve, with the aid of sonication, in 40 mL of a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 0.1). Dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 15-cm column that contains 4-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	100	0	equilibration
0–15	100→50	0→50	linear gradient
15–20	50→100	50→0	linear gradient
20–30	100	0	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for phthalic acid and about 1.0 for thalidomide; the tailing factor for the phthalic acid and thalidomide peaks is not more than 2.0; and the relative standard deviation determined from the phthalic acid peak for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 200 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 each impurity in the portion of Thalidomide taken by the formula:

~~$500(C_P / W)(r_i / r_P)$,~~

$$\blacktriangle 50{,}000(C_P / W)(r_i / r_P), \blacktriangle_{USP29}$$

in which C_P is the concentration, in mg per mL, of phthalic acid in the *Standard solution; W* is the amount, in mg, of Thalidomide taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_P is the phthalic acid peak response obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.3% of total impurities is found.

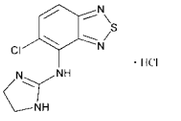
BRIEFING

Tizanidine Hydrochloride; Tizanidine Tablets. Because there are no existing *USP* monographs for this drug substance and dosage form, new monographs are being proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with a Luna C8 brand of L7 column. The retention time for tizanidine is about 6.7 minutes. The liquid chromatographic procedures in the test for *Related compounds* are based on analyses performed with a Symmetry C18 brand of L1 column. The retention time for tizanidine is about 5.5 minutes.

(PA3: R. Ravichandran) RTS—40316-3; 41493-1

Add the following:

▲Tizanidine Hydrochloride



$C_9H_8ClN_5S \cdot HCl$ 290.17

2,1,3-Benzothiadiazol-4-amine, 5-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, monohydrochloride.

In-Process Revision

5-Chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole monohydrochloride [*64461-82-1*].

» Tizanidine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_8ClN_5S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩**—***USP Tizanidine Hydrochloride RS. USP Tizanidine Related Compound A RS. USP Tizanidine Related Compound B RS. USP Tizanidine 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.*

pH ⟨791⟩**:** between 4.3 and 5.3, in a 1% (w/v) solution.

Loss on drying ⟨731⟩**—**Dry about 0.5 g of sample at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals ⟨231⟩**:** 0.002%.

Related compounds—

Phosphoric acid solution—Transfer 6.0 mL of phosphoric acid to a 50-mL volumetric flask, and dilute with water to volume.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water, and adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine 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 per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine 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 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C 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 per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution, Tizanidine related compound B solution,* and *Tizanidine related compound C solution.* Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Tizanidine 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 0.046 mg per mL.

Test solution—Transfer about 57 mg of Tizanidine Hydrochloride, 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 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1;* the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 4.0, and the resolution, *R,* between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 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—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 analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tizanidine Hydrochloride taken by the formula:

$$(253.71/290.17)5000(C/W)F(r_i/r_S),$$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of sample taken to prepare the *Test solution; F* is the relative response factor and is given in *Table 1;* r_i is the peak area for each impurity obtained from the *Test solution;* and r_S is the peak area of tizanidine obtained from the *Standard solution.* The limits for the impurities are specified in *Table 1.*

Table 1.

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.1
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	0.9	0.1
Tizanidine related compound A	about 10.2	0.9	0.1
Individual unknown	—	1.0	0.1
Total	—	—	0.3

In-Process Revision

Organic volatile impurities ⟨467⟩**:** meets the requirements.

Content of chloride—Dissolve about 500 mg, accurately weighed, in 50 mL of water. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride. Not less than 11.9% and not more than 12.5%, calculated on the dried basis, is found.

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5.3 N potassium hydroxide to a pH of 7.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve suitable quantities of USP Tizanidine Hydrochloride RS and USP Tizanidine Related Compound C RS in *Mobile phase*, and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 0.00012 mg per mL and 0.046 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine 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 0.046 mg per mL.

Assay preparation—Transfer about 23 mg of Tizanidine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 10.0 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 230-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for tizanidine related compound C and 1.0 for tizanidine; the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 13.0; and the tailing factor for the tizanidine peak is not more than 1.6. 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 responses for the major peaks. Calculate the quantity, in mg, of $C_9H_8ClN_5S \cdot HCl$ in the portion of Tizanidine Hydrochloride taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride 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.▲*USP29*

In-Process Revision

BRIEFING

Tizanidine Tablets—See briefing under *Tizanidine Hydrochloride*. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with a Symmetry C18 brand of L1 column. The retention time for tizanidine is about 5.5 minutes.

(PA3: R. Ravichandran) RTS—40316-2

Add the following:

▲Tizanidine Tablets

» Tizanidine Tablets contain Tizanidine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of tizanidine ($C_9H_8ClN_5S$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Tizanidine Hydrochloride RS. USP Tizanidine Related Compound A RS. USP Tizanidine Related Compound B RS. USP Tizanidine Related Compound C 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.]

Related compounds—

Phosphoric acid solution, Buffer solution, Mobile phase, Tizanidine related compound A solution, Tizanidine related compound B solution, Tizanidine related compound C solution, Resolution solution, and *Chromatographic system—*Proceed as directed in the *Assay.*

*Standard solution—*Prepare as directed for the *Standard preparation* 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 20 mg of tizanidine, to a 100-mL volumetric flask, add about 50 mL of *Buffer solution,* sonicate for about 15 minutes with occasional shaking, and shake on a shaker for 15 minutes. Add 20 mL of acetonitrile, and mix. Allow to cool, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of this solution at 2000 rpm or higher for 10 minutes. Pass a portion of this solution through a filter having a 45-µm or finer porosity, and use the filtrate.

*Procedure—*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 analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$(253.71/290.17)10{,}000(C/W)(A/D)F(r_i/r_s),$$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard solution; A* is the average weight, in mg, of each Tablet; D is the labeled dose, in mg, of tizanidine per Tablet; W is the weight, in mg, of sample taken to prepare the *Test solution; F* is the relative response factor and is given in *Table 1;* r_i is the peak area for each impurity obtained from the *Test solution;* and r_s is the peak area of tizanidine in the *Standard solution*. The limits for the impurities are specified in *Table 1.*

In-Process Revision

Table 1.

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.2
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	0.9	0.2
Tizanidine Related compound A	about 10.2	0.9	0.2
Individual unknown	—	1.0	0.2
Total	—	—	0.5

Assay—

Phosphoric acid solution—Dilute 6 mL of phosphoric acid with water to make 50 mL of solution.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water. Adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine 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 per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine 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 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C 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 per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution, Tizanidine related compound B solution,* and *Tizanidine related compound C solution.* Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine 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 0.046 mg per mL.

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 tizanidine, to a 500-mL volumetric flask, add about 250 mL of *Buffer solution,* sonicate for about 15 minutes with occasional shaking,

and shake on a shaker for 15 minutes. Add 100 mL of acetonitrile, and mix. Allow to cool, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of this solution at 2000 rpm or higher for 10 minutes. Pass a portion of this solution through a filter having a 45-µm or finer porosity, and use the filtrate.

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 packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1*; the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 4.0, and the resolution, *R,* between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 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 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 tizanidine ($C_9H_8ClN_5S$) in the portion of Tablets taken by the formula:

$$(253.71/290.17)500C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride 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.▲*USP29*

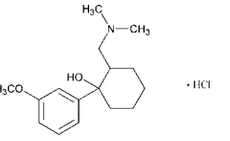
BRIEFING

Tramadol Hydrochloride. Because there is no existing *USP* monograph for this article, the following new monograph, which is based on submitted data, is being proposed. The liquid chromatographic procedure in the test for *Related compounds* is based on analyses performed with a LiChrospher 60 RP-select B brand of L1 column. The typical retention time for tramadol is about 16 minutes. The gas chromatographic procedure in the test for *Limit of isopropyl alcohol* is based on analyses performed with an Rtx-1301 brand of G43 column. The typical retention time for isopropyl alcohol is about 11 minutes.

(PA2: D. Bempong; NL: W. Paul; PSD: C. Okeke) RTS—37475-1; 37658-1

Add the following:

▲Tramadol Hydrochloride



$C_{16}H_{25}NO_2 \cdot HCl$ 299.84

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.

(±)-*cis*-2-[(Dimethylamino)methyl]-1-(*m*-methoxyphenyl) cyclohexanol hydrochloride [*36282-47-0*].

» Tramadol Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $C_{16}H_{25}NO_2 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Tramadol Hydrochloride RS. USP Tramadol Related Compound A RS. USP 2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride RS.*

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Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: An aqueous solution (1 in 100) meets the requirements of the test for *Chloride* ⟨191⟩.

Acidity—Dissolve 1 g in 20 mL of water. To each of two 5-mL portions of this solution, add 5 mL of water and 0.1 mL of methyl red TS. When 0.25 mL of 0.01 N sodium hydroxide is added to one portion, a yellow color is produced; and when 0.25 mL of 0.01 N hydrochloric acid is added to the other portion, a red color is produced.

pH ⟨791⟩**:** between 5.0 and 6.5, in a solution (1 in 100).

Loss on drying ⟨731⟩**—**Dry it at 105° 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 I* ⟨231⟩**:** 0.001%.

Limit of isopropyl alcohol—

Internal standard stock solution—Accurately weigh about 200 mg of *n*-propyl alcohol into a 20-mL volumetric flask containing about 15 mL of water, dilute with water to volume, and mix.

Internal standard solution—Transfer 2 mL of *Internal standard stock* solution to a 200-mL volumetric flask containing about 150 mL of water, dilute with water to volume, and mix.

Standard stock solution—Dissolve an accurately weighed quantity of isopropyl alcohol in *Internal standard solution*, and dilute quantitatively, and stepwise if necessary, with *Internal standard solution* to obtain a solution having a concentration of about 1.0 mg per mL.

Standard solution—Transfer 4 mL of the *Standard stock solution* to a 20-mL volumetric flask, and dilute with *Internal standard solution* to volume. Transfer 1 mL of the solution to a headspace vial, seal immediately, and mix gently.

Test solution—Transfer about 100 mg of Tramadol Hydrochloride, accurately weighed, to a headspace vial, add 1 mL of *Internal standard solution,* seal immediately, and mix gently.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a headspace sampler, and a 0.53-mm × 60-m fused silica column that contains 3-µm packing G43. The injection port is maintained at a temperature of about 140°; the column temperature is maintained at about 35° for 10 minutes, then increased by 10° per minute to 220° and maintained at 220° for 6 minutes; and the detector temperature is maintained at about 260°. The carrier gas is helium with a split flow (1 : 1) and a flow rate of 4.0 mL per minute. The headspace conditions are as follows. Incubation temperature is about 80°, incubation time is 30 minutes, syringe heater temperature is about 85°, sample volume is about 1 mL, fill speed is about 100 µL per second, and injection speed is about 2 mL per second. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for isopropyl alcohol and 1.3 for *n*-propyl alcohol; the resolution, *R,* between isopropyl alcohol and *n*-propyl alcohol is not less than 10.0; and the relative standard deviation, determined from the peak area ratio of isopropyl alcohol to *n*-propyl alcohol for three injections of the *Standard solution,* is not more than 2.0%.

Procedure—Inject the *Standard solution* and the *Test solution* into the gas chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of isopropyl alcohol in the portion of Tramadol Hydrochloride taken by the formula:

$$100(C/W)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of isopropyl alcohol in the *Standard solution; W* is the weight, in mg, of Tramadol Hydrochloride taken to prepare the *Test solution;*

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and R_U and R_S are the ratios of the peak responses of the corresponding isopropyl alcohol and internal standard peaks obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.2% of isopropyl alcohol is found.

Limit of 2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride—

Adsorbent—0.25-mm layer of chromatographic silica gel mixture.

Test solution—Transfer about 500 mg of Tramadol Hydrochloride, accurately weighed, into a 10-mL volumetric flask, and dilute with methanol to volume.

Standard solution—Dissolve an accurately weighed quantity of USP 2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 0.05 mg per mL.

Developing solvent system—Prepare a mixture of toluene, isopropyl alcohol, and 25% ammonia water (80 : 19 : 1).

Sodium nitrite solution—Dissolve about 2.5 g of sodium nitrite, accurately weighed, in 50 mL of water.

Procedure—Apply separately about 10 µL of the *Test solution* and the *Standard solution* to the plate, and develop the plate until the solvent front is 10 cm above the line of application. Remove the plate, spray with Dragendorff's TS, and air-dry for 5 minutes. Spray the dried plate with *Sodium nitrite solution* until the spot from 2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride in the *Standard solution* is visible. Any secondary spot in the chromatogram obtained from the *Test solution* corresponding to 2-(dimethylaminomethyl)-1-cyclohexanone hydrochloride is not more intense than a corresponding spot in the chromatogram obtained from the *Standard solution* (0.1%).

Related compounds—

Solution A—Dissolve 5 mL of perchloric acid in 950 mL of water in a 1-L volumetric flask, add 4 mL of 25% ammonia water, dilute with water to volume, and mix. Adjust with 25% ammonia water to a pH of 2.2 ± 0.2 . Filter and degas.

Solution B—Prepare a filtered and degassed solution of acetonitrile and water (9 : 1).

Diluent—Prepare a mixture of *Solution A* and acetonitrile (77 : 23).

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 in *Diluent* containing 4 µg of USP Tramadol Hydrochloride RS and 4 µg of USP Tramadol Hydrochloride Related Compound A RS per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Tramadol Hydrochloride RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 4 µg per mL.

System sensitivity solution—Transfer 2 mL of *Standard solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 200 mg of Tramadol Hydrochloride, accurately weighed, to a 50-mL volumetric flask; dissolve in and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 273-nm detector and a 4.0-mm × 25-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	77	23	equilibration
0–10	77	23	isocratic
10–30	77→33	23→67	linear gradient
30–35	33	67	isocratic
35–37	33→77	67→23	linear gradient
37–50	77	23	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tramadol and tramadol related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for each compound. Chromatograph the *System sensitivity solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10%.

Procedure—Inject a volume (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 Tramadol Hydrochloride taken by the formula:

$$5(C/W)(1/F)(r_i / r_S),$$

in which C is the concentration, in µg per mL, of USP Tramadol Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Tramadol Hydrochloride taken to prepare the *Test solution; F* is the relative response factor (see the accompanying table for values); r_i is the peak response obtained for each individual impurity in the *Test solution*; and r_S is the peak response for tramadol in the *Standard solution*. The limits of impurities are specified in the accompanying table.

Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (w/w, %)
RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohexanol hydrochloride (Tramadol related compound A)	about 0.89	1.00	0.1
Tramadol hydrochloride	1.00	—	—
1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-1-ene hydrochloride	about 1.50	1.00	0.1
1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-6-ene hydrochloride	about 1.46	1.14	0.1
3-Bromoanisole	about 1.80	1.42	0.1
3,3′-Dimethoxybiphenyl	about 2.00	3.72	0.1
Anisole	about 1.40	1.90	0.1
3-Methoxyphenol	about 0.72	2.28	0.1
Individual unknown impurity	—	1.00	0.1
Total impurities	—	—	0.5

Assay—Transfer about 400 mg of Tramadol Hydrochloride, accurately weighed, to a suitable beaker, dissolve by stirring in 40 mL of mercuric acetate TS, and add 20 mL of glacial acetic acid. Titrate with 0.1 M perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 M perchloric acid is equivalent to 29.984 mg of $C_{16}H_{25}NO_2 \cdot HCl$.▲*USP29*

BRIEFING

Tramadol Hydrochloride Tablets. Because there is no existing *USP* monograph for this article, the following new monograph, which is based on submitted data, is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Symmetry brand of L7 column. The typical retention times for tramadol are about 8 minutes for the test for *Related compounds* and about 4 minutes for the *Assay.*

(PA2: D. Bempong; BPC: M. Marques; NL: W. Paul; PSD: C. Okeke) RTS—37475-2

Add the following:

▲Tramadol Hydrochloride Tablets

» Tramadol Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Tramadol Hydrochloride RS. USP Tramadol Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—Accurately weigh powdered Tablets, equivalent to about 200 mg of tramadol hydrochloride, into a 50-mL volumetric flask, add 20 mL of dichloromethane, and sonicate. Filter, and transfer the clear supernatant to a separating funnel. Extract the dichloromethane layer with two 10-mL portions of 2 N sodium hydroxide, and discard the aqueous layer. Dry the dichloromethane layer over anhydrous sodium sulfate, and filter. Evaporate this solution to dryness under a stream of nitrogen.

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; 900 mL.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Determine the amount of $C_{16}H_{25}NO_2 \cdot HCl$ dissolved by employing the following method.

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

Standard solution—Dissolve an accurately weighed quantity of USP Tramadol Hydrochloride RS in 0.1 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.055 mg per mL.

Test solution—Withdraw 9 mL from the dissolution vessel, and pass through a 0.80-µm glass fiber filter. Discard the first 3 mL of the filtrate.

Chromatographic system—Proceed 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 2.0%.

In-Process Revision

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 tramadol peak responses. Calculate the quantity, in mg, of $C_{16}H_{25}NO_2 \cdot HCl$ dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC},$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Tramadol Hydrochloride RS in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim in mg.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{16}H_{25}NO_2 \cdot HCl$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

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

Test preparation—Transfer one whole Tablet to a 100-mL volumetric flask, add 70 mL of 0.1 N hydrochloric acid, sonicate until the Tablet is completely disintegrated, and shake for 10 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter, discarding the first 20 mL of the filtrate. Transfer 10 mL of the clear filtrate into a 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.

Chromatographic system—Proceed as directed in the *Assay.* 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 *Test preparation* into the chromatograph, record the chromatograms, and measure the tramadol peak responses. Calculate the quantity, in mg, of $C_{16}H_{25}NO_2 \cdot HCl$ in the Tablet by the formula:

$$500C(r_U / r_S),$$

in which *C* is the concentration, in mg per mL, of USP Tramadol Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses of tramadol obtained from the *Test preparation* and the *Standard preparation,* respectively.

Related compounds—

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

Resolution solution—Dissolve accurately weighed quantities of USP Tramadol Hydrochloride RS and USP Tramadol 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 0.2 mg per mL USP Tramadol Hydrochloride RS and about 0.2 mg per mL USP Tramadol Related Compound A RS.

Standard solution—Dissolve an accurately weighed quantity of USP Tramadol 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 6 µg per mL.

System sensitivity solution—Transfer 5 mL of the *Standard solution* into a 100-mL volumetric flask, dilute with *Mobile phase* 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 200 mg of tramadol hydrochloride, into a 50-mL volumetric flask, add about 35 mL of *Mobile phase,* sonicate for about 5 minutes, and shake for 10 minutes. Dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a suitable filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 273-nm detector and a 3.9-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution* and the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tramadol related compound A and tramadol is not less than 2.0; and the relative standard deviation for replicate injections of the *Standard solution* is not more than 2.0%. Chromatograph the *System sensitivity solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10%.

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 Tablets taken by the formula:

$$0.1(C_S/C_U)(1/F)(r_i/r_S),$$

in which C_S is the concentration, in µg per mL, of USP Tramadol Hydrochloride RS in the *Standard solution*; C_U is the concentration, in mg per mL, of tramadol hydrochloride in the *Test solution* based on the labeled quantity per tablet; F is the relative response factor (see the accompanying table for values); r_i is the peak response obtained for each individual impurity in the *Test solution;* and r_S is the peak response for tramadol in the *Standard solution*. [NOTE—Disregard any peak that is shown to be due to solvents or excipients.] The limits of impurities are specified in the accompanying table.

Compound Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (w/w, %)
RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohexanol hydrochloride (tramadol related compound A)	about 0.85	1.00	0.2
Tramadol hydrochloride	1.00	—	—
1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-1-ene hydrochloride	about 5.27	1.00	0.2
1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-6-ene hydrochloride	about 4.27	1.27	0.2
Individual unknown impurity	—	1.00	0.15
Total impurities	—	—	0.7

Assay—

Solution A—Dissolve 5 mL of perchloric acid in 950 mL of water in a 1-L volumetric flask, add 4 mL of 25% ammonia water, dilute with water to volume, and mix. Adjust with 25% ammonia water to a pH of 2.2 ± 0.2.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and acetonitrile (77 : 23). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Tramadol Hydrochloride RS in 0.1 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 50 mg of tramadol hydrochloride, into a 100-mL volumetric flask, add about 70 mL of 0.1 N hydrochloric acid, sonicate for about 5 minutes, and shake for 10 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter, discarding the first 20 mL of the filtrate. Transfer 10 mL of the clear filtrate into a 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 273-nm detector and a 3.9-mm × 15-cm column that contains packing L7. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections of the *Standard preparation* 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 tramadol peaks. Calculate the quantity, in mg, of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the portion of Tablets taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Tramadol 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.▲*USP29*

BRIEFING

Tricitrates Oral Solution, *USP 28* page 1971—See briefings under *Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation* and *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

(PA4: E. Gonikberg; D. Bempong) RTS—42196-9

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.*▲*USP29*

(Official January 1, 2009)

Change to read:

Assay for citrate—

~~*Cation exchange column*—Mix 10 g of styrene divinylbenzene cation exchange resin with 50 mL of water in a suitable beaker. Allow the resin to settle, and decant the supernatant until a slurry of resin remains. Pour the slurry into a 15-mm × 30-cm glass chromatographic tube (having a sealed-in, coarse-porosity fritted disk and fitted with a stopcock), and allow to settle as a homoge-~~

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~~neous bed. Wash the resin bed with about 100 mL of water, closing the stopcock when the water level is about 2 mm above the resin bed.~~

~~*Procedure*—Pipet 15 mL of Oral Solution into a 250-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution carefully onto the top of the resin bed in the *Cation-exchange column*. Place a 250-mL conical flask below the column, open the stopcock, and allow to flow until the solution has entered the resin bed. Elute the column with 60 mL of water at a flow rate of about 5 mL per minute, collecting about 65 mL of eluate. Add 5 drops of phenolphthalein TS to the eluate, swirl the flask, and titrate with 0.02 N sodium hydroxide VS. Record the buret reading, and calculate the volume *(B)* of 0.02 N sodium hydroxide consumed. Each mL of the difference between the volume *(B)* and the volume *(A)* of 0.02 N sodium hydroxide consumed in the *Assay for citric acid* is equivalent to 1.261 mg of $C_6H_8O_7$.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Pipet 15 mL of Oral Solution into a suitable volumetric flask, and proceed as directed under *Assay Preparation for Citric Acid/Citrate Assay* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩, and calculate the concentration, in mg per mL, of citrate ($C_6H_5O_7^{-3}$) in the Oral Solution taken by the formula:

$$0.001C_S(D/V)(r_U/r_S)-A(189.10/210.14),$$

in which C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; *V* is the volume of Oral Solution used in the preparation of the *Assay preparation;* r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively; 189.10 is the molecular weight of citrate ($C_6H_5O_7^{-3}$); 210.14 is the molecular weight of citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$); and *A* is the concentration of citric acid monohydrate, in mg per mL, determined in the *Assay for citric acid.*▲*USP29*

(Official January 1, 2009)

BRIEFING

Water for Injection, *USP 28* page 2033 and page 1650 of *PF* 30(5) [Sept.–Oct. 2004]; **Purified Water,** *USP 28* page 2035 and page 1316 of *PF* 30(4) [July–Aug. 2004]. At its meeting on December 8, 2004, the Pharmaceutical Waters Expert Committee decided to clarify the Definition in accordance with comments received.

(PW: F. Barletta) RTS—42233-1

Change to read:

» Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or ~~comparable~~

▲with the drinking water▲*USP29*
regulations of the European Union, Japan,

▲or with the World Health Organization's Guidelines for Drinking Water Quality.▲*USP29*
It contains no added substance.

NOTE—Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Water for Injection sterile and thereafter protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and, thereafter, protect it from microbial contamination. The tests for *Total organic carbon* and *Water conductivity* apply to Water for Injection produced on site for use in manufacturing. Water for Injection packaged in bulk for commercial use elsewhere meets the requirement of the test for *Bacterial endotoxins* as indicated below and the requirements of all the tests under *Sterile Purified Water,* except *Labeling*.

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Change to read:

Bacterial endotoxins ⟨85⟩—It contains ~~not more~~

■less■2S (*USP28*)
than 0.25 USP Endotoxin Unit per mL.

BRIEFING

Purified Water, *USP 28* page 2035 and page 1316 of *PF* 30(4) [July–Aug. 2004]—See briefing under *Water for Injection.*

(PW: F. Barletta) RTS—42233-2

Change to read:

» Purified Water is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or ~~comparable~~

▲with the drinking water▲*USP29*
regulations of the European Union, Japan,

▲or with the World Health Organization's Guidelines for Drinking Water Quality.▲*USP29*
It contains no added substance.

NOTE—Purified Water is intended for use as an ingredient of official preparations and in tests and assays unless otherwise specified (see *Water* in *Ingredients and Processes* and in *Tests and Assays* under *General Notices and Requirements*). Where used for sterile dosage forms, other than for parenteral administration, process the article to meet the requirements under *Sterility Tests* ⟨71⟩, or first render the Purified Water sterile and thereafter protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection. The tests for *Total organic carbon* and *Conductivity* apply to Purified Water produced on site for use as an ingredient of official preparations and in tests and assays. Purified Water packaged in bulk for commercial use elsewhere meets the requirements of all of the tests under *Sterile Purified Water,* except *Labeling* and *Sterility* ⟨71⟩.

BRIEFING

Pure Steam, page 1651 of *PF* 30(5) [Sept.–Oct. 2004]. The Pharmaceutical Waters Expert Committee met on December 8, 2004, and addressed all of the comments received. This amended proposal clarifies the intent of the monograph relative to the application of Pure Steam so as to differentiate it from other types of steam used in the pharmaceutical industry.

(PW: F. Barletta) RTS—41332-1

Add the following:

▲Pure Steam

NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.

» Pure Steam is water that has been heated above 100° and vaporized in a manner that prevents source water entrainment. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations, or with drinking water regulations of the European Union or Japan, or with WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of noncondensable gases are to be determined by the Pure Steam application.

NOTE—Pure Steam is intended for use where the steam or its condensate comes in contact with the article or the preparation. Pure Steam quality is difficult to assess in its vapor state; therefore the attributes of its condensate are used to ~~indirectly~~

test its quality. The process used to create and collect the condensate for analysis must not adversely impact these quality attributes.

USP Reference standards ⟨11⟩—*USP 1,4 Benzoquinone RS. USP Endotoxin RS. USP Sucrose RS.*

Bacterial endotoxins ⟨85⟩—The condensate contains less than 0.25 USP Endotoxin Unit per mL (when used in the production of parenterals).

Total organic carbon ⟨643⟩**:** the condensate meets the requirement.

Water conductivity ⟨645⟩**:** the condensate meets the requirement.▲*USP29*

BRIEFING

Water for Hemodialysis, *USP 28* page 2036 and page 1317 of *PF* 30(4) [July–Aug. 2004]. At its December 8, 2004 meeting, the Pharmaceutical Waters Expert Committee decided that the test for *Oxidizable substances* should be performed in the same manner in all USP monographs in which it is required. This change is proposed in accordance with this decision.

(PW: F. Barletta) RTS—42235-1

Change to read:

Bacterial endotoxins ⟨85⟩—It contains ~~not more~~

■less■1S *(USP28)*
than 2 USP Endotoxin Units per mL.

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2 N sulfuric acid, and heat to boiling. Add ~~0.1 mL~~

▲0.2 mL▲*USP29*
of ~~0.1 N~~

▲0.02 N▲*USP29*

potassium permanganate, and boil for 5 minutes. The pink color does not completely disappear; or alternatively follow the test method for *Total Organic Carbon* ⟨643⟩.

BRIEFING

Zinc Sulfate Oral Solution. Because there is no existing *USP* monograph for this drug product, the following new monograph is being proposed. The development of this monograph has been requested by the United Nations International Children's Emergency Fund (UNICEF), the United States Agency for International Development (USAID), and the World Health Organization (WHO) as a treatment for diarrhea. Although the product is not approved by the FDA, USP is giving this monograph special consideration to support efforts by the aforementioned organizations to ensure the availability of quality public standards for the product marketed outside the USA.

(DSN: L. Evans; PSD: C. Okeke; NL: C. Barnstein) RTS—41920-1; 41994-1

Add the following:

▲Zinc Sulfate Oral Solution

» Zinc Sulfate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of zinc sulfate ($ZnSO_4 \cdot H_2O$). It may contain one or more suitable flavors and sweeteners.

Packaging and storage—Preserve in well-closed containers protected from light, and store in a cool, dry place.

Labeling—Label the Oral Solution in terms of zinc sulfate ($ZnSO_4 \cdot H_2O$) and in terms of elemental zinc.

Identification—The Oral Solution responds to the tests for *Zinc* ⟨191⟩ and for *Sulfate* ⟨191⟩.

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pH ⟨791⟩**:** between 2.5 and 4.5.

Specific gravity ⟨841⟩**:** between 1.18 and 1.24.

Assay—Transfer to a 250-mL flask an accurately measured volume of Oral Solution, equivalent to about 99 mg of $ZnSO_4 \cdot H_2O$. Add 50 mL of water and 10 mL of ammonia–ammonium chloride buffer TS and 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS to a green endpoint. Each mL of 0.05 M edetate disodium is equivalent to 8.973 mg of zinc sulfate ($ZnSO_4 \cdot H_2O$). ▲*USP29*

DIETARY SUPPLEMENTS—MONOGRAPHS

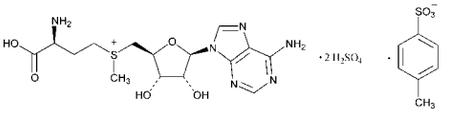
BRIEFING

Ademetionine Disulfate Tosylate, page 2075 of *PF* 29(6) [Nov.–Dec. 2003]. On the basis of comments received, this new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision* with a revised title and additional modifications. The use of a surrogate reference standard is being proposed to deal with the instability and potency challenges attributed to the chiral sulfonium on the ademetionine molecule. Increased instability at ambient temperatures and in the presence of humidity initiates degradation. Ademetionine containing the double salts sulfate and tosylate improves stability but does not resolve the problem. In addition, the tosylate counterion is nonstoichiometric, with significant variation between the moles of tosylate per mole of ademetionine. These problems are alleviated using as a surrogate reference standard USP *S*-Adenosyl-L-Homocysteine RS, which lacks the methyl group on the sulfur, the cause of instability in the molecule. The HPLC method being proposed in the *Assay* uses the surrogate reference standard in a reverse-phase HPLC method based on analyses performed with the Luna C18 brand of L1 column. In the test for *Isomeric ratio*, it is proposed to revise the previously published specification. A specification of not less than 60% and the labeled amount of the *S,S*-isomer is being proposed. Although it has been extensively reported that only the *S,S*-isomer is enzymatically active for transmethylation, studies indicate that racemization of the *S,S*-isomer to the *R,S*-isomer readily occurs, causing the formation of the *R,S*-isomer, present at levels as low as 20% and increasing with time to 40%. Stability data could help to resolve this issue by establishing a requirement for an expiry date on the label to ensure the quality of the material; however, USP has not received such data and is requesting this information from manufacturers. Additional data is also being requested to identify and establish limits for impurities not given in the proposed *Related compounds* test.

(DSN: L. Evans) RTS—41179-1; 41234-1; 41639-1; 41664-1; 41667-1; 41667-2; 41667-3; 41667-4; 41668-1; 42214-1; 42227-1

Add the following:

▲~~*S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate~~ Ademetionine Disulfate Tosylate



$C_{22}H_{34}N_6O_{16}S_4$ ~~766.56~~ 766.80

S-(Adenosyl)-L-methionine disulfate ~~*p*-toluene sulfonate~~ tosylate.

(3*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulfonio]-5′-deoxyadenosine ~~hydroxide~~, disulfate-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~~

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~~the dried basis.~~ Ademetionine Disulfate Tosylate is the disulfate–tosylate mixed salt of a mixture of diastereoisomers of the ademetionine ions. It contains not less than 95.0 percent and not more than 105.0 percent of ademetionine ($C_{15}H_{23}N_6O_5S^+$), calculated on the anhydrous 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.*~~ *USP Ademetionine Disulfate Tosylate RS. USP S-Adenosyl-L-Homocysteine RS.*

Labeling—Label it to indicate the minimum content, in percentage, of *S,S*-isomer.

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%.~~ 3.0%.

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

Organic volatile impurities ~~*Method V*~~ ⟨~~467~~⟩**:** ~~not more than 0.001%~~ meets the requirements.

Isomeric ratio—

Buffer A—Transfer 4.2 g of citric acid monohydrate and 2.03 g of 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*~~ *preparation* and *Test* ~~*solution*~~ *preparation*—Use the ~~*Standard preparation*~~ and the ~~*Assay preparation*~~ *Standard solution* and the *Test solution,* prepared as directed in ~~*Assay*~~ *Related compounds.*

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*~~ *preparation,* 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,~~ the *R,S*- and *S,S*-isomers, respectively.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard* ~~*solution*~~ *preparation* and the *Test* ~~*solution*~~ *preparation* 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 the *R,S*-isomer, respectively, in the *Test solution*. Not less than ~~75%~~ 60% and not less than the labeled amount of the *S,S*-isomer is found.

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Related compounds—

Mobile phase— ~~Prepare as directed in the *Assay.*~~ 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 solution—Dissolve an accurately weighed quantity of USP Ademetionine Disulfate Tosylate RS in water to obtain a solution having a known concentration of 1.0 mg per mL.

Test solution— ~~Use the *Assay preparation.*~~ Transfer about 100 mg of Ademetionine Disulfate Tosylate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— ~~Prepare as directed in the *Assay.* Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure.*~~ 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 solution,* 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—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~~ Ademetionine Disulfate Tosylate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area for each individual impurity; and 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~~ 3.0
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~~ Ademetionine Disulfate Tosylate, 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 and 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 is not less than 8200 theoretical plates; the tailing factor is not more than ~~1.1~~ 1.5; 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 area of the sulfate peak. Calculate the percentage of sulfate in the portion of ~~*S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate~~ Ademetionine Disulfate Tosylate 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~~ Ademetionine Disulfate Tosylate 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. The content of sulfate is not less than 23.5% and not more than 26.5%.

Content of ~~*p*-toluene sulfonic acid~~ tosylate—

Mobile phase and *Chromatographic system*—~~Proceed as directed in the *Assay.*~~ Proceed as directed in *Related compounds.*

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.~~ *Mobile phase.*

Test solution—Transfer about 100 mg of ~~*S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate~~ Ademetionine Disulfate Tosylate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system—Prepare as directed in ~~*Assay*~~ *Related compounds.* 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 area of the ~~*p*-toluene sulfonic acid~~ tosylate peak. Calculate the percentage of ~~*p*-toluene sulfonic acid~~ tosylate in the portion of ~~*S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate~~ Ademetionine Disulfate Tosylate taken by the formula:

$$\sout{10{,}000}\ 5000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of tosylate ion in the *Standard solution; W* is the weight, in mg, of ~~*S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate~~ Ademetionine Disulfate Tosylate taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained for ~~*p*-toluene sulfonic acid~~ tosylate in the chromatograms of the *Test solution* and the *Standard solution,* respectively. The content of tosylate is not less than 21% and not more than 24%.

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 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~~

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~~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 $C_{14}H_{22}N_6O_5S$ 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.~~

Buffer—Transfer 10 mL of glacial acetic acid to a 1-L volumetric flask, add 500 mL of water, and mix. To the flask add 2.06 g of sodium 1-hexanesulfonate, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed solution of *Buffer* and acetronitrile (85 : 15).

System suitability solution—Dissolve accurately weighed quantities of USP Ademetionine Disulfate Tosylate RS and USP *S*-Adenosyl-L-Homocysteine RS in water to obtain a solution having concentrations of about 400 µg of each per mL.

Standard preparations—Dissolve an accurately weighed quantity of USP *S*-Adenosyl-L-Homocysteine RS in water to obtain *Standard preparation A,* having a known concentration of about 400 µg per mL. Dilute portions of *Standard preparation A* to obtain *Standard preparation B* and *Standard preparation C,* having known concentrations of about 200 µg and 80 µg per mL, respectively.

Assay preparation—Transfer about 20 mg of Ademetionine Disulfate Tosylate, accurately weighed, to a 50-mL volumetric flask, add 40 mL of water, and stir for 30 minutes; then dilute with water to volume, and mix. Transfer 1.0 mL of the solution to a 1.5-mL microcentrifuge tube, and centrifuge for 1 minute. Use a portion of the supernatant as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and *Standard preparation B,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.68 for *S*-adenosyl-L-homocysteine and 1.0 for ademetionine disulfate tosylate; the resolution, *R*, between *S*-adenosyl-L-homocysteine and ademetionine disulfate tosylate is not less than 1.5; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% for *S*-adenosyl-L-homocysteine in *Standard preparation B*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparations* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area of the *S*-adenosyl-L-homocysteine peak in all three solutions and the ademetionine disulfate tosylate peak in the *Assay preparation.* Plot a calibration curve of the peak area of the *Standard preparations* versus the corre-

sponding *S*-adenosyl-L-homocysteine concentration, in mg per mL, and draw the straight line best fitting the three points. From the calibration curve, and using the peak area of ademetionine from the chromatogram obtained with the *Assay preparation,* determine the concentration, *C,* of ademetionine as *S*-adenosyl-L-homocysteine in the *Assay preparation.* Calculate the quantity, in mg, of ademetionine ($C_{15}H_{23}N_6O_5S^+$) in the portion of Ademetionine Disulfate Tosylate taken by the formula:

$$50C(399.44/384.41),$$

in which 399.44 and 384.41 are the molecular weights of ademetionine and *S*-adenosyl-L-homocysteine, respectively. ▲*USP29*

BRIEFING

Fish Oil Rich in Omega-3 Acids, page 1272 of *PF* 29(4) [July–Aug. 2003]. On the basis of comments received, this proposed new monograph is being presented again with a revised title and additional modifications.

(DSN: L. Evans) RTS—42065-1

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Add the following:

▲Fish Oil ~~Rich in~~ Containing Omega-3 Acids

» Fish Oil ~~Rich in~~ Containing 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 (w/w) of total omega-3 acids, expressed as ~~triglycerides,~~ free acids, 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, and store at controlled room temperature. It may be bottled or otherwise packaged in containers from which air has been expelled by production of a 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.

USP Reference standards ⟨11⟩—~~*USP Cod Liver Oil RS.*~~ *USP Fish Oil RS. USP Methyl Tricosanoate RS. USP Omega-3 Ethyl Esters 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*~~ *Test solution* in the test for *Content of EPA and DHA* correspond to those for the respective compounds in the chromatogram of the *Standard solutions.* The sum of the area for EPA and DHA methyl esters is not less than ~~28~~ 22% 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*~~ the *Test solution* exhibits at least 15 additional peaks at the retention times of the methyl esters of unsaturated fatty acids exhibited in the chromatogram of *Standard solution 2.*

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%.

Stearin: 100 mL remains clear after cooling at 0° for 3 hours.

Absorbance—Dilute 0.300 g to 50.0 mL with isooctane. Quantitively transfer 2.0 mL of this solution to a 50-mL volumetric flask, and dilute with isooctane to volume. The absorbance is 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.]

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.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard stock solution—Transfer 10.0 mL of *Standard Arsenic Solution,* prepared as directed in the test for *Arsenic* ⟨211⟩, 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 the *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*

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protection and protective clothing and gloves.] Transfer approximately 500 mg of Fish Oil Containing Omega-3 Acids, 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. [NOTE—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 percent 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.

Procedure—Program the graphite furnace as follows. Dry at 115°, using a 1-second ramp, a 65-second hold, and an argon flow of 300 mL per minute; char the sample at 1000°, using a 1-second ramp, a 20-second hold, and an air flow of 300 mL per minute; cool down, and purge the air from the furnace for 10 seconds, using a 20° set temperature and an argon flow of 300 mL per minute; atomize at 2400°, using a 0-second ramp and a 5-second hold with the argon flow stopped; and clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Standard solutions,* the *Test solution,* and the *Blank,* followed by an injection of 5 µL of the *Modifier working solution* for each of the samples, 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 portion of Fish Oil Containing Omega-3 Acids taken by the formula:

$$25C/W,$$

in which W is the weight, in g, of Fish Oil Containing Omega-3 Acids 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, to 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, to a Teflon beaker. Add 40 mL of water and 1 mL of nitric acid, and

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warm on a hot plate to dissolve the solids. Allow the solution to cool to room temperature, transfer it to 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* to 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.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

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.

Standard solutions—Dilute the *Standard stock solution* with the *Blank* to obtain solutions containing, respectively, 0.002, 0.005, 0.010, 0.025, and 0.050 µg per mL of lead.

Test solution—Prepare as directed for *Test solution* in the test for *Limit of arsenic.*

Procedure—Program the graphite furnace as follows. Dry at 120°, using a 1-second ramp, a 55-second hold, and an argon flow of 300 mL per minute; char the sample at 850°, using a 1-second ramp, a 30-second hold, and an air flow of 300 mL per minute; cool down, and purge the air from the furnace for 10 seconds, using a 20° set temperature and an argon flow of 300 mL per minute; atomize at 2100°, using a 0-second ramp and a 5-second hold with the argon flow stopped; and clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Standard solutions,* the *Test solution,* and the *Blank,* followed by an injection of 5 µL of the *Modifier working solution* for each of the samples, 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 portion of Fish Oil Containing Omega-3 Acids taken by the formula:

$$25C/W,$$

in which W is the weight, in g, of Fish Oil Containing Omega-3 Acids 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 dihydrogen phosphate stock solution—Transfer 10 g of ultrapure ammonium dihydrogen phosphate, accurately weighed, to 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, to 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 to 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* to a 10-mL volumetric flask, and dilute with 2% nitric acid to volume. A volume of 5 µL provides 0.2 mg of phosphate and 0.01 mg of magnesium nitrate.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard stock solution—Transfer 137.2 mg of cadmium nitrate to a 1000-mL volumetric flask, dissolve in and 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.

Standard solutions—Dilute the *Standard stock solution* with the *Blank* to obtain solutions containing, respectively, 0.002, 0.005, 0.010, 0.025, and 0.050 µg per mL of cadmium.

Test solution—Prepare as directed for *Test solution* in the test for *Limit of arsenic.*

Procedure—Program the graphite furnace as follows. Dry at 120°, using a 1-second ramp, a 55-second hold, and an argon flow of 300 mL per minute; char the sample at 850°, using a 1-second ramp, a 30-second hold, and an air flow of 300 mL per minute; cool down, and purge the air from the furnace for 10 seconds, using a 20° set temperature and an argon flow of 300 mL per minute; atomize at 2400°, using a 0-second ramp and a 5-second hold with the argon flow stopped; and clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Standard solutions,* the *Test solution,* and the *Blank,* followed by an injection of 5 µL of the *Modifier working solution* for each of the samples, 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 each mL of the *Test solution* by interpolation from the regression line. Calculate the content of cadmium in the Fish Oil Containing Omega-3 Acids taken by the formula:

$$25C/W,$$

in which W is the weight, in g, of Fish Oil Containing Omega-3 Acids taken to prepare the *Test solution:* not more than 0.1 µg per g is found.

Limit of mercury—Proceed as directed for *Method IIb* under *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.* The limit is 0.1 µg per g.

Limit of ~~pesticides~~ dioxins, furans, and polychlorinated biphenyls (PCBs)—Determine the content of polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)~~, and polychlorinated biphenyls (PCBs) using the Environmental Protection Agency's Method No. 1613, Revision B.~~ by method No. 1613 revision B of the Environmental Protection Agency. Determine the content of polychlorinated biphenyls (PCBs) by method No. 1668 revision A of the Environmental Protection Agency. The sum of polychlorinated dibenzo-*para*-dioxins (PCDDs)

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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~~ equivalents per g. The amount of dioxin-like PCBs (polychlorinated biphenyls, non-ortho IUPAC congeners PCB-77, PCB-81, PCB-126, and PCB-169, and mono-ortho IUPAC congeners PCB-105, PCB-114, PCB-118, PCB-123, PCB-156, PCB-157, PCB-167, and PCB-189) is not more than 3 pg of WHO toxic equivalents 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.

Internal standard solution—Transfer an accurately weighed quantity ~~of about 70.0 mg~~ of USP Methyl Tricosanoate RS to a ~~10 mL~~ volumetric flask. Dissolve in ~~isooctane~~ *Antioxidant solution*, and dilute with the same solvent to ~~volume~~ obtain a solution having a concentration of about 3.5 mg per mL. [NOTE—Guard the solution against evaporation during usage.]

~~*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 stock solution 1—Transfer 0.100 g of USP Omega-3 Ethyl Esters RS, accurately weighed, to a 10-mL volumetric flask, and dissolve in and dilute with *Internal standard solution* to volume.

Standard stock solution 2—Proceed as directed for *Standard stock solution 1,* but use 0.300 g of USP Fish Oil RS instead of USP Omega-3 Ethyl Esters RS.

~~*Standard solution*~~ *Standard solution 1*—Transfer 2.0 mL of ~~the *Standard stock solution*~~ *Standard stock solution 1* to 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 boiling water bath for 7 minutes. Cool, add 2 mL of boron trichloride–methanol solution, cover with nitrogen, cap tightly, mix, and heat in a boiling water bath for 30 minutes. Cool to 40° to 50°, add 1 mL of isooctane, cap, and mix on 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 on 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 combined extracts with two quantities, each of 1 mL of water, and dry over anhydrous sodium sulfate.

Standard solution 2—Proceed as directed for *Standard solution 1,* but use *Standard stock solution 2* instead of *Standard stock solution 1.*

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 1895-1AMP.]

Test stock solution—Transfer 0.300 g of Fish Oil ~~Rich in~~ Containing Omega-3 Acids, accurately weighed, to a 10-mL volumetric flask, and dissolve in and dilute with *Internal standard solution* to volume.

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~~*Test solution 1*—Proceed as directed for the *Standard solution,* using the *Stock test solution–Standard solution 1,* except to use the *Test stock solution* and to omit the addition of the *Internal standard 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.*~~ Proceed as directed for *Standard solution 1,* except to use the *Test stock solution.*

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° for 2 minutes, then increased at a rate of ~~1°~~ 3° per minute to ~~225°, and is maintained at 225°~~ 240°, and is maintained at this temperature for 20 minutes. The carrier gas is helium with a split flow ratio of 1 : 200. [NOTE—If splitless injection mode is used, solutions should be further diluted 1 in 200.] Chromatograph ~~the *Standard solution,*~~ *Standard solution 2,* the *System suitability mixture,* ~~*Test solution 1,* and *Test solution 2,*~~ and the *Test solution,* and record the peak responses as directed for *Procedure:* the resolution between the peaks in ~~the Standard solution~~ *Standard solution 2* due to methyl oleate and methyl *cis*-vaccinate is not less than 1.3. ~~and that between methyl gadoleate and methyl gondoate is sufficient for purposes of identification and area measurement.~~ The theoretical area percentages ~~for~~ in the chromatogram of the *System suitability mixture* 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% of the total area in the chromatogram of ~~the *Standard solution*~~ *Standard solution 2* is at least 24, and the 24 largest peaks of the methyl esters account for more than 90% of the total area. (These correspond, in common elution order, to: 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*~~ the *Internal standard solution, Standard solution 1, Standard solution 2,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Identify the retention times of the relevant fatty acid methyl esters by comparison of the chromatogram of ~~the *Standard solution,*~~ *Standard solution 2* with the reference chromatogram supplied with the ~~USP Cod Liver Oil RS.~~ USP Fish Oil RS. Identify the retention time for the *Internal standard solution* ~~by comparison of the chromatograms of *Test solution 1* and *Test solution 2*~~ by comparing the chromatograms for the *Internal standard solution* and *Standard solution 1*. Calculate the area percentage 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 of the *Test solution,* excepting the solvent front and butylated hydroxytoluene. Calculate the percentage of

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EPA or DHA in the Fish Oil ~~Rich in~~ Containing Omega-3 Acids taken by the formula:

~~$500FC(r_i/r_s)/1.04W,$~~

$$1000C/W(R_U/R_S),$$

in which 1000 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*~~ either DHA or EPA in *Standard solution 1; W* is the weight, in mg, of the Fish Oil ~~Rich in~~ Containing Omega-3 Acids taken to prepare the *Test stock 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;*~~ R_U is the ratio of peak responses of either EPA or DHA relative to the internal standard in the chromatogram of ~~*Test solution 2*~~ the *Test solution;* ~~and r_s is the corrected peak response of the internal standard in *Test solution 2* calculated as follows:~~

~~$[(r_{s2}/r_{EPA2}) - (r_{s1}/r_{EPA1})]r_{EPA1},$~~

~~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.*~~ and R_S is the ratio of peak responses of either EPA or DHA relative to the internal standard in *Standard solution 1.* ▲*USP29*

BRIEFING

Fish Oil Rich in Omega-3 Acids Capsules, page 1278 of *PF* 29(4) [July–Aug. 2003]. On the basis of comments received, this proposed new monograph is being presented again with a revised title and additional modifications.

(DSN: L. Evans) RTS—42065-2

Add the following:

▲Fish Oil ~~Rich in~~ Containing Omega-3 Acids Capsules

» Fish Oil ~~Rich in~~ Containing 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~~ Containing Omega-3 Acids. The oil contained in Fish Oil ~~Rich in~~ Containing Omega-3 Acids Capsules conforms to the definition for *Fish Oil ~~Rich in~~ Containing Omega-3 Acids.*

Packaging and storage—Preserve in tight containers, and store at room temperature. Protect from light.

Labeling—The label states the amount of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in mg per Capsule.

USP Reference standards ⟨11⟩ ~~*USP Cod Liver Oil RS.*~~ *USP Fish Oil RS. USP Methyl Tricosanoate RS. USP Omega-3 Ethyl Esters RS.*

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Identification—Proceed as directed for *Identification* under *Fish Oil ~~Rich in~~ Containing 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 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 *Acid value, Anisidine value, ~~Heavy metals,~~ Peroxide value, Total oxidation value, Unsaponifiable matter, Stearin, Absorbance, Limit of arsenic, Limit of lead, Limit of cadmium, Limit of mercury, ~~and Pesticides~~* and *Limit of dioxins, furans, and polychlorinated biphenyls* under *Fish Oil ~~Rich in~~ Containing 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 EPA and DHA—Proceed as directed for *Content of EPA and DHA* under *Fish Oil ~~Rich in~~ Containing Omega-3 Acids*.▲*USP29*

BRIEFING

Selenomethionine, *USP 28* page 2130. It is proposed to add USP L-Methionine RS to the *USP Reference standards* section and to correct the name of the Reference Standard to L-Methionine in the *System suitability preparation* in the *Assay.*

(DSN: L. Evans) RTS—42251-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP L-Methionine RS.*▲*USP29*
USP Selenomethionine RS.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed solution of 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 2.75 ± 0.25. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve suitable quantities of ~~USP Methionine RS~~

▲USP L-Methionine RS▲*USP29*
and USP Selenomethionine RS in *Mobile phase* to obtain a solution containing about 0.8 mg per mL and 0.16 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Selenomethionine RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.16 mg per mL.

Assay preparation—Transfer about 40 mg of Selenomethionine, accurately weighed, to a 250-mL volumetric flask, dissolve in *Mobile phase* with sonication, dilute with *Mobile phase* to volume, and mix. Filter through a 0.45-µm membrane.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and 4.6-mm × 25-cm column that contains packing L1 with polar end-capping. The flow rate is about 1.0 mL per minute. Chromat-

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ograph the *System suitability preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for methionine and 1.0 for selenomethionine; the resolution, *R,* between methionine and selenomethionine is not less than 3.0; 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* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_5H_{11}NO_2Se$ in the portion of Selenomethionine taken by the formula:

$$25C/W(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Selenomethionine RS in the *Standard preparation; W* is the weight, in g, of the portion of Selenomethionine 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.

MONOGRAPHS (NF)

BRIEFING

Ammonio Methacrylate Copolymer Dispersion, *NF 23* page 2956. It is proposed to delete *Identification* test *B* because the requirements for the *Viscosity* test and *Assay* are already included in the monograph.

(EMC: C. Sheehan) RTS—42108-1

Change to read:

Identification—

~~**A:**~~

▲▲*NF24*

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.*~~

▲▲*NF24*

BRIEFING

Purified Bentonite, *NF 23* page 2962. The proposed revision to the *Assay for aluminium and magnesium content* is based on comments received that the current *Magnesium standard preparations* concentrations of 50 ppm to 200 ppm are too high, considering that a magnesium concentration of less than 1 ppm is obtained if the magnesium content of the *Test preparation* is about 3%. Therefore, a further dilution of the 1 mg per mL *Magnesium standard stock preparation* is necessary before preparing the four working standard solutions. In addition, minor editorial style changes have been made.

(EMC: C. Sheehan) RTS—42194-1

Change to read:

Assay for aluminum and magnesium content—[NOTE—The *Standard preparations* and *Assay preparations* may be diluted quantitatively with water, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Lanthanum solution—Stir 88.30 g of lanthanum chloride ($LaCl_3$) with 500 mL of 6 N hydrochloric acid until solution is complete, transfer with the aid of water to a 1000-mL volumetric flask, and dilute with water to volume.

Test preparation—Transfer 0.200 g of Purified Bentonite to a 25-mL platinum crucible containing 1.0 g of lithium metaborate, and mix. Using a muffle furnace or a suitable burner, heat slowly at first, and ignite at 1000° to 1200° for 15 minutes. Cool, place the crucible in a 100-mL beaker containing 25 mL of dilute nitric acid (1 in 20), and add an additional 50 mL of the dilute acid, filling and submerging the upright crucible. Place a polyfluorocarbon-coated magnetic stirring bar into the crucible, and stir gently with a magnetic stirrer until solution is complete. Pour the contents into a 250-mL beaker, and remove the crucible. Warm the solution, and transfer through a rapid-flow filter paper with the aid of water into a 200-mL volumetric flask, dilute with water to volume, and mix.

Aluminum standard stock preparation—Dissolve 1.000 g of aluminum in a mixture of 10 mL of hydrochloric acid and 10 mL of water by gentle heating. Transfer the solution to a 1000-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 1 mg of aluminum per mL.

Aluminum standard preparations—Transfer 2-, 5-, and 10-mL aliquots of the *Aluminum standard stock preparation* to separate 100-mL volumetric flasks containing 200 mg of sodium chloride, dilute each with water to volume, and mix.

Aluminum assay preparation—Pipet 20 mL of *Test preparation* into a 100-mL volumetric flask. Add 20 mL of a solution of sodium chloride (1 in 100), dilute with water to volume, and mix.

Procedure for aluminum—In a suitable atomic absorption spectrophotometer equipped with an aluminum hollow-cathode lamp and a single-slot burner, using an oxidizing air–acetylene–nitrous oxide flame, determine the absorbances of the *Aluminum assay preparation* and each of the *Aluminum standard preparations* at 309 nm. From a linear regression equation calculated from the absorbances and concentrations of the *Aluminum standard preparations*, determine the aluminum content of the Purified Bentonite.

Magnesium standard stock preparation—Place 1.000 g of magnesium in a 250-mL beaker containing 20 mL of water, and carefully add 20 mL of hydrochloric acid, warming, if necessary, to complete the reaction. Transfer the solution to a 1000-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 1 mg of magnesium per mL.

▲Transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with water to volume, and mix.▲*NF24*

Magnesium standard preparations—Transfer 5-, 10-, 15-, and 20-mL aliquots of the *Magnesium standard stock preparation* to separate 100-mL volumetric flasks. To each flask add 20.0 mL of *Lanthanum solution,* dilute with water to volume, and mix.

Magnesium assay preparation—Transfer a 25-mL aliquot of *Test preparation* to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer a 5.0-mL aliquot of this dilution to a 100-mL volumetric flask, add 20.0 mL of *Lanthanum solution,* dilute with water to volume, and mix.

Procedure for magnesium—In a suitable atomic absorption spectrophotometer equipped with a magnesium hollow-cathode lamp and a single-slot burner, using a reducing acetylene–air flame, determine the absorbances of the *Magnesium assay preparation* and each of the *Magnesium standard preparations* at 285 nm. From a linear regression equation calculated from the absorbances and concentrations of the *Magnesium standard preparations,* determine the magnesium content of the Purified Bentonite: the ratio of the aluminum content to the magnesium content is between 3.5 and 5.5.

BRIEFING

Carbomer 934, *NF 23* page 2972—See briefing under *Carbomer Copolymer.*

(EMC: E. Gonikberg, C. Sheehan; NL: W.L. Paul) RTS—41274-4

Change to read:

Labeling—Label it to indicate that it is not intended for internal use.

▲A carbomer homopolymer manufactured using benzene and complying with the unique requirements of this monograph will be officially titled Carbomer 934 and will not be referred to as *Carbomer Homopolymer.*▲*NF24*

BRIEFING

Carbomer 934P, *NF 23* page 2973. On the basis of comments received, it is proposed to revise the test for *Limit of benzene* to change the maximum column temperature and ramp rate in the *Chromatographic system* to coincide with the requirements in *Method V* under *Organic Volatile Impurities* ⟨467⟩. It is also proposed to reduce the injection volume in the *Procedure* from 4 µL to 1 µL. See also the briefing under *Carbomer Copolymer.*

(EMC: C. Sheehan, E. Gonikberg; NL: W.L. Paul) RTS—38241-1; 41274-5

Add the following:

▲**Labeling**—A carbomer homopolymer manufactured using benzene and complying with the unique requirements of this monograph will be officially titled Carbomer 934P and will not be referred to as *Carbomer Homopolymer.*▲*NF24*

Change to read:

Limit of benzene—

Standard solution—Dissolve an accurately weighed quantity of benzene quantitatively 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 about 1 g of Carbomer 934P, accurately weighed, to a 100-mL volumetric flask. Add about 75 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogenous (usually about 30 minutes). Dilute with sodium chloride solution (2 in 100) to volume, and mix until homogenous (usually less than 1 minute). [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 temperatures 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, then increased ~~at 50° per minute to 260°, and held at 260° for 20 minutes.~~

▲rapidly to 240°, and maintained at 240° for 20 minutes.▲*NF24*

Chromatograph the *Standard solution,* and record the 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)~~

▲(about 1 µL)▲*NF24*

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of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the benzene peaks. Calculate the percentage of benzene in the portion of Carbomer 934P 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 934P 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 0.01% is found.

BRIEFING

Carbomer 940, *NF 23* page 2973 and page 1328 of *PF* 30(4) [July–Aug. 2004]—See briefing under *Carbomer Copolymer.*

(EMC: C. Sheehan, E. Gonikberg; NL: W. L. Paul) RTS—41274-6

Change to read:

Labeling—Label it to indicate that it is not intended for internal use.

▲A carbomer homopolymer manufactured using benzene and complying with the unique requirements of this monograph will be officially titled Carbomer 940 and will not be referred to as *Carbomer Homopolymer.*▲*NF24*

Change to read:

Viscosity—Proceed as directed in the test for *Viscosity* under *Carbomer 934P,* except to use a spindle having a shaft 0.32 cm in diameter, the distance from the top of the shaft to the lower tip of the shaft being 5.04 cm, and the immersion depth being ~~0.95 cm~~

■5.6 cm■ IS *(NF23)*
(No. 7 spindle). The viscosity is between 40,000 and 60,000 centipoises.

BRIEFING

Carbomer 941, *NF 23* page 2974—See briefing under *Carbomer Copolymer.*

(EMC: C. Sheehan, E. Gonikberg; NL: W.L. Paul) RTS—41274-7

Change to read:

Labeling—Label it to indicate that it is not intended for internal use.

▲A carbomer homopolymer manufactured using benzene and complying with the unique requirements of this monograph will be officially titled Carbomer 941 and will not be referred to as *Carbomer Homopolymer.*▲*NF24*

BRIEFING

Carbomer 1342, *NF 23,* page 2974—See briefing under *Carbomer Copolymer.*

(EMC: C. Sheehan, E. Gonikberg; NL: W.L. Paul) RTS—41274-8

Change to read:

Labeling—Label it to indicate that it is not intended for internal use.

▲A carbomer copolymer manufactured using benzene and complying with the unique requirements of this monograph will be officially titled Carbomer 1342 and will not be referred to as *Carbomer Copolymer.*▲*NF24*

BRIEFING

Carbomer Copolymer, *NF 23* page 2974; **Carbomer Homopolymer,** page 2013 of *PF* 29(6) [Nov.–Dec. 2003]; **Carbomer Interpolymer,** *NF 23* page 2976; **Carbomer 934,** *NF 23* page 2972; **Carbomer 934P,** *NF 23* page 2973; **Carbomer 940,** *NF 23* page 2973 and page 1328 of *PF* 30(4) [July–Aug. 2004]; **Carbomer 941,** *NF 23* page 2974; **Carbomer 1342,** *NF 23* page 2974. On the basis of comments received, it is proposed to make the following changes:

1. Revise the Definition and *Labeling* under *Carbomer Homopolymer* and *Carbomer Copolymer* to clearly define that these monographs cover only carbomers manufactured without using benzene as a solvent. Add a statement under *Labeling* for *Carbomer 934, Carbomer 934P, Carbomer 940,* and *Carbomer 941* to clarify that these monographs cover carbomers manufactured with the use of benzene, which will not be referred to as *Carbomer Homopolymer.* Similarly, add a statement under *Labeling* for *Carbomer 1342* to clarify that this monograph covers a carbomer manufactured with the use of benzene, which will not be referred to as *Carbomer Copolymer.*
2. Clarify the Definition for *Carbomer Copolymer* and *Carbomer Homopolymer* by replacing the term ''polyalkenyl ethers'' with ''allyl ethers''.
3. Add a test for *Limit of benzene* and establish a strict limit of benzene (not more than 2 ppm) for *Carbomer Copolymer, Carbomer Homopolymer,* and *Carbomer Interpolymer.*
4. Add a test for *Organic volatile impurities* (*Method IV*) to *Carbomer Copolymer, Carbomer Homopolymer,* and *Carbomer Interpolymer.*
5. In the test for *Content of carboxylic acid* under *Carbomer Copolymer,* delete the reference to the pH value at the titration endpoint to make the method consistent with the currently official method under *Carbomer 934P.* This change also affects *Carbomer Homopolymer* and *Carbomer Interpolymer.*

In addition, there are also some editorial changes.

(EMC: E. Gonikberg, C. Sheehan; NL: W. L. Paul) RTS—41274-2

Change to read:

» Carbomer Copolymer is a high molecular weight copolymer of acrylic acid and a long chain alkyl methacrylate cross-linked with ~~polyalkenyl~~

▲allyl▲*NF24*
ethers of polyalcohols.

NOTE—

▲The heading of this monograph does not constitute the official title for a *Carbomer Copolymer* manufactured with the use of benzene. When benzene is used in the manufacturing process, the name will be *Carbomer 1342,* provided it complies with the existing requirements in the *Carbomer 1342* monograph.▲*NF24*

Different types of Carbomer Copolymers may not have identical properties with respect to their use for specific pharmaceutical purposes, e.g., as controlled-release agents, bioadhesives, topical gels, thickening agents, and emulsifying agents. Therefore, different types of Carbomer Copolymers should not be interchanged unless performance equivalency has been ascertained.

Change to read:

Labeling— ~~Label it to indicate the nominal viscosity range and~~

▲If benzene has been used in the manufacturing process, the name of the article will be *Carbomer 1342,* provided it complies with and is labeled in accordance with the requirements set forth in that monograph. If benzene is not used in the manufacturing process, label it to indicate whether it is Type A, B, or C; and also to state▲*NF24*
the measured viscosity, the solvent or solvents used in the polymerization process, and the nominal and residual solvent levels for each solvent.

Add the following:

▲**Limit of benzene**—[NOTE—This test does not apply to articles labeled *Carbomer 1342.* Those articles meet a different set of requirements for *Limit of benzene* found in the monograph for *Carbomer 1342*.]

Solvent solution—Dissolve an accurately weighed quantity of benzene quantitatively in dimethyl sulfoxide to obtain a solution having a concentration of about 1.0 mg per mL. Dilute this solution quantitatively, and stepwise if necessary, with organic-free water (see *Organic Volatile Impurities* ⟨467⟩) to obtain a solution having a concentration of about 0.1 µg per mL.

Test solution—Transfer about 50 mg of Carbomer Copolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Dilute with sodium chloride solution

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(2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). [NOTE—This preparation must be analyzed within 3 hours of preparation.]

Reference solution—Transfer about 50 mg of Carbomer Copolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Add 1.0 mL of the *Solvent solution,* dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). This solution contains about 0.01 µg of benzene per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, flame-ionization detector, and a 0.53-mm × 30-m fused silica analytical column coated with a 3.0-µm G43 stationary phase. The carrier gas is helium flowing at a linear velocity of about 35 cm per second, and the split ratio is 1 : 5. The injection port and detector temperatures are maintained at 140° and 250°, respectively. The column temperature is programmed according to the following steps: it is held at 40° for 20 minutes after injection, then increased at 10° per minute to 240°, and held at 240° for 20 minutes. [NOTE—The following headspace conditions may be used: a pressurization time of 30 seconds and a transfer line temperature of 90°.] The vials are maintained at a temperature of 80° for 60 minutes prior to headspace injection. Chromatograph the *Reference solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for three replicate injections is not more than 15%.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Transfer 10.0 mL each of the *Reference solution* and the *Test solution* to separate headspace vials. Close the vials with a tight rubber membrane stopper coated with polytetrafluoroethylene, and secure with an aluminum crimped cap. Shake to obtain a homogeneous dispersion. Separately inject equal volumes (about 1 mL) of the gaseous phase of the *Reference solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the benzene peaks. Calculate the percentage of benzene in the portion of Carbomer Copolymer taken by the formula:

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

in which C is the concentration, in µg per mL, of benzene in the *Reference solution; W* is the weight, in mg, of Carbomer Copolymer taken to prepare the *Test solution;* and r_U and r_S are the benzene peak responses obtained from the *Test solution* and the *Reference solution,* respectively: not more than 0.0002% is found.▲*NF24*

Add the following:

▲**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements for chloroform, 1,4-dioxane, methylene chloride, and trichloroethylene.▲*NF24*

Change to read:

Content of carboxylic acid—Slowly add about 400 mg of Carbomer Copolymer, previously dried in vacuum at 80° for 1 hour and accurately weighed, to 400 mL of water in a 1000-mL beaker, while stirring continually at about 1000 rpm. The stirrer shaft is set at an angle of about 60° and to 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 system, titrate potentiometrically with 0.25 N sodium hydroxide VS ~~to a pH of 10.0~~

▲▲*NF24*
(see *Titrimetry* ⟨541⟩). After each addition of 0.25 N sodium hydroxide VS, allow 1 minute for mixing before recording the pH. Calculate the percentage of carboxylic acid in the portion of Carbomer Copolymer taken by the formula:

$$100(45.02VN/W),$$

in which 45.02 is the molecular weight of the carboxylic acid (–COOH) group; V is the volume, in mL, of sodium hydroxide consumed; N is the normality of the sodium hydroxide solution; and W is the weight, in mg, of Carbomer Copolymer taken. The carboxylic acid content is not less than 52.0% and not more than 62.0%.

BRIEFING

Carbomer Homopolymer, page 2013 of *PF* 29(6) [Nov.–Dec. 2003]. See briefing under *Carbomer Copolymer.* In addition, it is proposed to revise the test for *Loss on drying* to lower the limit to 2.0%.

(EMC: E. Gonikberg, C. Sheehan; NL: W.L.Paul) RTS—41274-1

Add the following:

▲Carbomer Homopolymer

» Carbomer Homopolymer is a high molecular weight polymer of acrylic acid cross-linked with ~~polyalkenyl~~ allyl 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.~~ The heading of this monograph does not constitute the official title for a Carbomer Homopolymer manufactured with the use of benzene. When benzene is used in the manufacturing process, the name of the article will be Carbomer 934, Carbomer 934P, Carbomer 940, or Carbomer 941, whichever is appropriate. Carbomer Homopolymer obtained from different manufacturers or produced in different solvents with different manufacturing 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.~~ If benzene has been used in the manufacturing process, the name of the article will be Carbomer 934, Carbomer 934P, Carbomer 940, or Carbomer 941, whichever is appropriate. In addition, when benzene is used, the labeling requirements for the referenced individual Carbomer are applicable. If benzene is not used in the manufacturing process, 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⟩—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.

~~**B:** The viscosity test result complies with the viscosity range indicated on the label.~~

~~**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.

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~~**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.

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%~~ 2.0% 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.

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. Chro-

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~~matograph 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.~~ [NOTE—This test does not apply to those articles titled *Carbomer 934*, *Carbomer 934P*, *Carbomer 940* or *Carbomer 941*. Those articles meet the requirements for *Limit of benzene* in their respective individual monographs.]

Solvent solution—Dissolve an accurately weighed quantity of benzene quantitatively in dimethyl sulfoxide to obtain a solution having a concentration of about 1.0 mg per ml. Dilute this solution quantitatively, and stepwise if necessary, with organic-free water (see *Organic Volatile Impurities* ⟨467⟩) to obtain a solution having a concentration of about 0.1 µg per mL.

Test solution—Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 ml of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). [NOTE—This preparation must be analyzed within 3 hours of preparation.]

Reference solution—Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Add 1.0 mL of the *Solvent solution*, dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). This solution contains about 0.01 µg of benzene per mL.

Chromatographic system—Proceed as directed in the test for *Limit of benzene* under *Carbomer Copolymer.*

Procedure—Proceed as directed in the test for *Limit of benzene* under *Carbomer Copolymer*. Calculate the percentage of benzene 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 benzene in the *Reference 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 *Reference solution,* respectively: not more than 0.0002% is found.

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements for chloroform, 1,4-dioxane, methylene chloride, and trichloroethylene.

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).

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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⟩).

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 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.

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~~

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~~the carboxylic acid (–COOH) group.~~ Proceed as directed in the test for *Content of carboxylic acid* under *Carbomer Copolymer,* except to calculate the percentage of carboxylic acid in the portion of Carbomer Homopolymer taken by the formula:

$$100(45.02VN/W),$$

in which W is the weight, in mg, of the portion of Carbomer Homopolymer taken; and the other terms are as defined therein.▲*NF24*

BRIEFING

Carbomer Interpolymer, *NF 23* page 2976—See briefing under *Carbomer Copolymer.*

(EMC: E. Gonikberg, C. Sheehan; NL: W.L. Paul) RTS—41274-3

Change to read:

Labeling—Label it to indicate ~~the nominal viscosity range and~~ ▲whether it is Type A, B, or C; and also to state▲*NF24* the measured viscosity, the solvent or solvents used in the polymerization process, and the nominal and measured residual solvent levels for each solvent.

Add the following:

▲**Limit of benzene**—

Solvent solution—Quantitatively dissolve an accurately weighed quantity of benzene in dimethyl sulfoxide to obtain a solution having a concentration of about 1.0 mg per mL. Dilute this solution quantitatively, and stepwise if necessary, with organic-free water (see *Organic Volatile Impurities* ⟨467⟩) to obtain a solution having a concentration of about 0.1 µg per mL.

Test solution—Transfer about 50 mg of Carbomer Interpolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). [NOTE—This preparation must be analyzed within 3 hours of preparation.]

Reference solution—Transfer about 50 mg of Carbomer Interpolymer, accurately weighed, to a 10-mL volumetric flask. Add about 7.5 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (usually about 30 minutes). Add 1.0 mL of the *Solvent solution,* dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (usually less than 1 minute). This solution contains about 0.01 µg of benzene per mL.

Chromatographic system—Proceed as directed in the test for *Limit of benzene* under *Carbomer Copolymer.*

Procedure—Proceed as directed in the test for *Limit of benzene* under *Carbomer Copolymer.* Calculate the percentage of benzene in the portion of Carbomer Interpolymer taken by the formula:

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

in which C is the concentration, in µg per mL, of benzene in the *Reference solution; W* is the weight, in mg, of Carbomer Interpolymer taken to prepare the *Test solution;* and r_U and r_S are the benzene peak responses obtained from the *Test solution* and the *Reference solution,* respectively: not more than 0.0002% is found.▲*NF24*

Add the following:

▲**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements for chloroform, 1,4-dioxane, methylene chloride, and trichloroethylene.▲*NF24*

BRIEFING

Cetostearyl Alcohol, *NF 23* page 2985. On the basis of comments received regarding the difficulty in meeting the current system suitability requirements in the *Assay,* it is proposed to revert to the requirements for relative standard deviation that were specified in the original version of the monograph.

(EMC: D. Bempong) RTS—42187-1

Change to read:

Assay—

System suitability 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.

Assay preparation—Dissolve 100 mg of Cetostearyl 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 column temperature is maintained at about 205°, the injection port temperature at about 275°, and the detector temperature 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%

▲for the percentages of $C_{16}H_{34}O$ and $C_{18}H_{38}O$.▲*NF24*

Procedure—Inject about 2 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Separately calculate the percentages of cetyl alcohol ($C_{16}H_{34}O$) and stearyl alcohol ($C_{18}H_{38}O$) in the portion of Cetostearyl Alcohol taken by the formula:

$$100(r_U / r_s),$$

in which r_U is the peak area obtained from cetyl alcohol or stearyl alcohol; and r_s is the sum of the areas of all the peaks, except the solvent peak.

BRIEFING

Cetyl Alcohol, *NF 23* page 2986 and page 970 of *PF* 30(3) [May–June 2004]. As a result of comments received regarding difficulty in meeting the revised system suitability requirements for the *Assay,* it is proposed to change the relative standard deviation to the original requirement.

(EMC: D. Bempong) RTS—42195-1

Change to read:

Assay—

System suitability solution—Dissolve accurately weighed quantities of USP Cetyl Alcohol RS and USP Stearyl Alcohol RS in ■dehydrated■1S *(NF23)* alcohol to obtain a solution having known concentrations of about 9 mg per mL and 1 mg per mL, respectively.

Assay preparation—Dissolve 100 mg of Cetyl 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 column temperature is maintained at about 205°, the injection port temperature is maintained at about 275°, and the detector temperature 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,

▲calculated with the area ratio of cetyl alcohol to stearyl alcohol,▲*NF24* 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 $C_{16}H_{34}O$ in the portion of Cetyl Alcohol taken by the formula:

$$100(r_U / r_s),$$

in which r_U is the peak area for cetyl alcohol obtained from the *Assay preparation;* and r_s is the sum of the areas of all the peaks except the solvent peak.

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BRIEFING

Glyceryl Monostearate, *NF 23* page 3015 and page 975 of *PF* 30(3) [May–June 2004]. On the basis of comments received, it is proposed to revise the *Assay for monoglycerides* to update the monograph with a size-exclusion liquid chromatographic method that is comparable to assay procedures for similar monographs. It is also proposed to delete the *USP Reference standards* section because no reference standard is used.

(EMC: J. Lane) RTS—42249-1

Delete the following:

▲~~**USP Reference standards** ⟨11⟩ — *USP Monoglycerides RS.*~~ ▲*NF24*

Change to read:

Hydroxyl value ⟨401⟩**:** between ~~300~~

■290■1S (*NF23*)
and 330.

Change to read:

Saponification value ⟨401⟩**:** between ~~155~~

■150■1S (*NF23*)
and 165.

Change to read:

Assay for monoglycerides—

~~*Propionating reagent*—Mix 10 mL of pyridine and 20 mL of propionic anhydride.~~

~~*Internal standard solution*—Transfer about 400 mg of hexadecyl hexadecanoate, accurately weighed, to a 100-mL volumetric flask, dissolve in chloroform, dilute with chloroform to volume, and mix.~~

~~*Standard preparation*—Transfer about 50 mg of USP Monoglycerides RS, accurately weighed, to a 25-mL conical flask, add by pipet 5 mL of *Internal standard solution,* and mix. When solution is complete, immerse the flask in a water bath maintained at a temperature between 45° and 50°, and volatilize the chloroform with the aid of a stream of nitrogen. Add 3.0 mL of *Propionating reagent,* and heat on a hot plate at 75° for 30 minutes. Evaporate the reagents with the aid of a stream of nitrogen and gentle steam heat. Add 15 mL of chloroform, and swirl to dissolve the residue.~~

~~*Assay preparation*—Transfer about 50 mg of Glyceryl Monostearate, accurately weighed, to a 25-mL conical flask, and proceed as directed for *Standard preparation,* beginning with "add by pipet 5 mL of *Internal standard solution*."~~

~~*Chromatographic system*—Under typical conditions the instrument is equipped with a flame-ionization detector, and contains a 4-mm × 2.4-m borosilicate glass column packed with 2% liquid phase G27 on 80- to 100-mesh support S1A. The column is maintained isothermally at a temperature between 270° and 280°, the injection port and detector block temperature are maintained at about 310°, and helium is used as the carrier gas at a flow rate of about 70 mL per minute.~~

~~*System suitability*—Chromatograph six to ten injections of the *Standard preparation* as directed for *Procedure:* the resolution factor, *R,* between the peaks for the derivatized glyceryl hexadecanoate and glyceryl octadecanoate is not less than 2.0, and the relative standard deviation of the ratio of the peak area of the derivatized glyceryl octadecanoate to that of the hexadecyl hexadecanoate is not more than 2.0%.~~

~~*Procedure*—Inject a suitable portion of the *Standard preparation* into a suitable gas chromatograph, and record the chromatogram. Measure the areas under the peaks, and record the values of the sum of the areas under the derivatized monoglyceride peaks and of the area under the hexadecyl hexadecanoate peak as A_s and A_u, respectively. Calculate the response factor, F, by the formula:~~

$$(A_s/A_u)(W_u/W_s),$$

~~in which W_u and W_s are the weights, in mg, of hexadecyl hexadecanoate and USP Monoglycerides RS, respectively, in the *Standard preparation.* Similarly inject a suitable portion of the *Assay preparation,* and record the chromatogram. Measure the areas under the peaks, and record the values of the sum of the areas under the derivatized monoglyceride peaks and of the area under the hexadecyl hexadecanoate peak as a_s and a_u, respectively. Calculate the quantity, in mg, of monoglycerides in the amount of Glyceryl Monostearate taken by the formula:~~

$$(W_u/F)(a_s/a_u),$$

~~in which the terms are as defined therein.~~

▲*Mobile phase*—Use tetrahydrofuran.

Assay preparation—Transfer about 40 mg of Glyceryl Monostearate, 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 7.5-mm × 60-cm column containing 5-µm 100-Å packing L21. The column and the detector temperatures are maintained at 40°. [NOTE—Two or three 7.5-mm × 30-cm L21 columns may be used in place of the one 60-cm column, provided that system suitability requirements are met; and the column temperature may be lowered to ambient temperature, although working at 40° provides stable separation conditions and ensures better sample solubility.] The flow rate is about 1 mL per minute. 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 di-

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glycerides, and 0.77 for triglycerides; and the relative standard deviation for replicate injections determined from the monoglycerides peak is not more than 2.0%.

Procedure—Inject a volume (about 40 µL) of the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of monoglycerides in the portion of Glyceryl Monostearate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for the monoglycerides; and r_s is the sum of the responses for all the glyceride peaks. ▲*NF24*

BRIEFING

Purified Honey. Because there is no existing *NF* monograph for this excipient, a new monograph based on submitted data is being proposed.

(EMC: D. Bempong; AMB: R. Tirumalai) RTS—33071-1; 31287-1

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Add the following:

▲Purified Honey

» Purified Honey is obtained by purification of honey from the comb of the bee, *Apis mellifera L.* and all subspecies of *Apis mellifera*. The honey is extracted by centrifugation, pressure, or other suitable procedures.

Packaging and storage—Preserve in tight containers. No storage requirements specified.

Labeling—Label it to indicate that it is not intended for use in preparations for infants under one year of age, unless it meets the requirement for *Clostridium* species.

USP Reference standards ⟨11⟩—*USP L-Proline RS.*

Identification—To a 0.5-mL aliquot of a solution (1 in 20) in a reaction vial add 0.25 mL of formic acid and 1.0 mL of freshly prepared 3% solution of ninhydrin in peroxide-free ethylene glycol monomethyl ether. Cap the reaction vial tightly, shake well, and place in boiling water for 15 minutes. Cool for 5 minutes in a 22° water bath, remove the cap, and add 5.0 mL of 5% aqueous isopropanol solution. The solution shows a purple color similar to, or more intense than, that of a similarly treated 7.5-µg-per-mL solution of USP L-Proline RS. If necessary, scan the solutions being compared using a suitable spectrophotometer against a water blank. The two solutions each exhibit a maximum at the same wavelength, at about 520 nm. The absorbance of the sample solution should be at least as high as that of the similarly treated 7.5-µg-per-mL solution of USP L-Proline RS.

Specific gravity ⟨841⟩**:** between 1.400 and 1.435 at 20°.

Refractive index ⟨831⟩**:** between 1.4900 and 1.4992 at 20°.

Microbial limits ⟨61⟩—The total bacterial count does not exceed 1000 cfu per g, the total combined molds and yeasts count does not exceed 100 cfu per g.

Clostridium species—Where it is intended for use in preparations for infants under one year of age, it meets the requirements for absence of *Clostridium* species in *Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements* ⟨2022⟩.

Water, *Method I* ⟨921⟩**:** between 15.0% and 18.6%.

Chloride ⟨221⟩—A 1-g portion shows no more chloride than corresponds to 0.5 mL of 0.020 N hydrochloric acid (0.035%).

Sulfate ⟨221⟩—A 2-g portion shows no more sulfate than corresponds to 0.5 mL of 0.020 N sulfuric acid (0.024%).

Total ash ⟨561⟩: not more than 0.3%.▲*NF24*

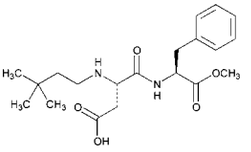
BRIEFING

Neotame. Because there is no existing *NF* monograph for this article, the following new monograph, which is based on submitted data, is being proposed. The liquid chromatographic procedures in the *Assay* and in the test for *Related compounds* are based on analysis performed with the Whatman Partisil 5 ODS 3, RAC II brand of L1. The typical retention time for neotame is about 12 minutes.

(EMC: D. Bempong; PSD: C. Okeke; NL: C. Barnstein)
RTS—41442-1

Add the following:

▲Neotame



$C_{20}H_{30}N_2O_5$ 378.47

L-Phenylalanine, *N*-[*N*-(3,3-dimethylbutyl)-L-α-aspartyl]-1-methyl ester.

N-[*N*-(3,3-Dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester [*165450-17-9*].

» Neotame contains not less than 97.0 percent and not more than 102.0 percent of $C_{20}H_{30}N_2O_5$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, store in a dry place, and avoid exposure to excessive heat.

USP Reference standards ⟨11⟩—*USP Neotame RS. USP Neotame Related Compound A RS.*

Identification, *Infrared Absorption* ⟨197K⟩.

Specific rotation ⟨781S⟩**:** between –40.0° and –43.4°, determined at 20°.

Test solution: 5 mg per mL, in water.

Water, *Method Ic* ⟨921⟩**:** not more than 5.0%.

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

Lead—[NOTE—Use acid-cleaned (mixture of 5% nitric acid and 5% hydrochloric acid followed by rinsing with water) autosampler cups and volumetric glassware to avoid contamination. For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin. Select all reagents to have as low a content of lead as practicable. Store standards and samples in acid-cleaned polyethylene containers.]

Diluent—Transfer 2 mL of lead-free nitric acid into a 1000-mL volumetric flask, dilute with water to volume, and mix.

Standard stock solution—Dissolve 79.9 mg of lead nitrate in 100 mL of *Diluent* in a 500-mL volumetric flask, and dilute with *Diluent* to volume. Transfer 10.0 mL of the resulting solution into a 100-mL volumetric flask, and dilute with *Diluent* to volume. Each mL of the *Standard stock solution* contains the equivalent of 10 µg of lead.

Standard solutions—Dilute aliquots of the *Standard stock solution* quantitatively and stepwise, if necessary, with *Diluent* to obtain solutions having concentrations of 0.03 and 0.015 µg per mL.

Test solution—Transfer 160 mg of Neotame, accurately weighed, to a 10-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume.

Blank—Use the *Diluent* as the blank.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard solutions*, the *Blank*, and the *Test solution* into a suitable graphite furnace atomic absorption spectrophotometer set at 283.3 nm and equipped with an autosampler, pyrolytically coated graphite tubes, solid pyrolytic graphite platform, and an adequate means of background correction. Use a hollow-cathode lamp as the source, use argon as the purge gas, and breathing-quality air as the alternate gas. Optimize the instrument program as recommended by the manufacturer for lead, using a char temperature of 500° and an atomization temperature of 2000°. Correct the area responses of all *Test solutions* and *Standard solutions* for the *Blank* area response. Generate the appropriate lead calibration algorithm, and determine the lead concentration in the *Test solution,* in µg per mL. Calculate the percentage of lead in the portion of Neotame taken by the formula:

$$1000(C/W),$$

in which C is the blank corrected lead concentration in the *Test solution,* in µg per mL; and W is the weight, in µg, of Neotame taken for the *Test solution:* not more than 0.0002% is found.

Related compounds—

Mobile phase—Proceed as directed in the *Assay.*

Related compound A standard solution—Dissolve an accurately weighed quantity of USP Neotame Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about 0.03 mg per mL.

Detector sensitivity solution—Transfer 2 mL of the *Related compound A standard solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

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

Test solution—Transfer about 100 mg of Neotame, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. [NOTE—This solution is stable for up to 32 hours when stored at a temperature of 0° to 10°.]

Chromatographic system (see *Chromatography* ⟨621⟩)—Use the same system as directed in the *Assay* except to chromatograph the *Related compound A standard solution* and the *Detector sensitivity solution*, and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the *Detector sensitivity solution* is not less than 10; and the relative standard deviation for replicate injections of the *Related compound A standard solution* is not more than 5.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Related compound A standard solution*, thr *Standard solution*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of related compound A in the portion of Neotame 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 Neotame Related Compound A RS in the *Related compound A standard solution;* C_U is the concentration, in mg per mL, of Neotame in the *Test solution;* and r_U and r_S are related com-

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pound A peak responses obtained from the the *Test solution* and *Related compound A standard solution,* respectively: not more than 1.5% is found. Calculate the percentage of other impurites in the portion of Neotame taken by the formula:

$$100(C_S/C_U)(A_i/A_S),$$

in which C_S is the concentration, in mg per mL, of USP Neotame RS in the *Standard solution;* and C_U is the concentration, in mg per mL, of Neotame in the *Test solution*; A_S is the response of the neotame peak in the *Standard solution*; and A_i is the sum of the responses of all impurity peaks (except that of related compound A and the solvent peak, if observed) in the *Test solution*: not more than 2.0% is found.

Assay—

Mobile phase—Dissolve 3.0 g of sodium 1-heptanesulfonate in 740 mL of water in a suitable 1000-mL vessel, add 3.8 mL of triethylamine, and mix. Adjust the resulting solution with phosphoric acid to a pH of 3.5, and dilute with water to 750 mL. Add 250 mL of acetonitrile, adjust with phosphoric acid to an apparent pH of 3.7, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Neotame 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.

Assay preparation—Transfer about 50 mg of Neotame, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5 mL of the resulting solution into a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. [NOTE—This solution is stable for up to 32 hours when stored at a temperature of 0° to 10°].

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 10-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 45°. 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 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 $C_{20}H_{30}N_2O_5$ in the portion of Neotame taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Neotame 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.▲*NF24*

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BRIEFING

Propylene Glycol Dilaurate. Because there is no existing *NF* monograph for this product, a new monograph, based on the Propylene Glycol Dilaurate monograph in the *European Pharmacopoeia, Fourth Edition,* page 4551, is being proposed.

(EMC: D. Bempong; NL: W. Paul; PSD: C. Okeke) RTS—42051-1

Add the following:

▲Propylene Glycol Dilaurate

Dodecanoic acid, monoester with 1,2-propanediol.

Lauric acid, monoester with propane-1,2-diol.

Propylene dilaurate.

» Propylene Glycol Dilaurate is a mixture of the propylene glycol mono- and di-esters of lauric acid. It contains not less than 70.0 percent of diesters and not more than 30.0 percent of monoesters.

Packaging and storage—Preserve in well-closed containers, and protect from moisture. No storage requirements specified.

USP Reference standards ⟨11⟩—*USP Propylene Glycol RS. USP Propylene Glycol Dilaurate RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution: 50 mg per mL, in methylene chloride.

Developing solvent solution: a mixture of hexane and ether (30 : 70)

Spray reagent—Prepare a 0.1 mg per mL solution of rhodamine 6G in alcohol.

Procedure—Develop the chromatogram over a path of 15 cm, and dry the plate in a current of air. Spray the plate with *Spray reagent,* and locate the spots on the plate by examination under UV light at a wavelength of 365 nm: the R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the Standard solution.

B: It complies with the requirements of the test for *Fatty acid composition.*

Acid value ⟨401⟩**:** not more than 4.

Iodine value ⟨401⟩**:** not more than 1.

Saponification value ⟨401⟩**:** between 230 to 250.

Fatty acid composition ⟨401⟩—Propylene Glycol Dilaurate exhibits the following composition profile of fatty acids, determined as directed in the chapter.

Fatty Acids	Carbon-Chain Length	Percentage (%)
Caprylic acid	C8	not more than 0.5
Capric acid	C10	not more than 2.0
Lauric acid	C12	not less than 95.0
Myristic acid	C14	not more than 3.0
Palmitic acid	C16	not more than 1.0

Water, *Method Ia* ⟨921⟩**:** not more than 1.0%, using a mixture of methanol and methylene chloride (1 : 1) in place of methanol in the titration vessel.

Total ash ⟨561⟩**:** not more than 0.1%.

Limit of propylene glycol—

Mobile phase—Proceed as directed in the *Assay.*

Propylene glycol standard stock solution—Prepare a solution containing a known concentration of about 4 mg per mL of USP Propylene Glycol RS in tetrahydrofuran.

Propylene glycol standard solutions—Into four 15-mL flasks, introduce respectively 0.25 mL, 0.5 mL, 1.0 mL, and 2.5 mL of *Propylene glycol standard stock solution,*

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and dilute with tetrahydrofuran to 5.0 mL. In a fifth 15-mL flask, introduce 5.0 mL of *Propylene glycol standard stock solution*.

Test solution—Use the *Assay preparation*.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 40 µL) of the *Propylene glycol standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Prepare a standard curve of peak area versus concentration, in mg per mL, of propylene glycol in the *Propylene glycol standard solutions*. Obtain the concentration, *C,* in mg per mL, of propylene glycol in the *Test solution* from the standard curve. Calculate the percentage of free propylene glycol in the portion of Propylene Glycol Dilaurate taken by the formula:

$$100CV/W,$$

in which V is the final volume of the *Test solution;* and W is the weight, in mg, of Propylene Glycol Dilaurate used to prepare the *Test solution:* not more than 2.0% is found.

Assay—

Mobile phase: tetrahydrofuran.

Assay preparation—Accurately weigh about 200 mg of Propylene Glycol Dilaurate into a 15-mL flask, add 5 mL of tetrahydrofuran, and shake to dissolve.

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 packing L21 (100Å). The flow rate is about 1 mL per minute. The column and detector temperatures are maintained at 40°. [NOTE—Two 7-mm × 30-cm L21 columns may be used in place of one 60-cm column, provided system suitability requirements are met.] Chromatograph the *Assay preparation,* and record the peak responses as directed for *Procedure*. The order of elution is diesters, monoesters, and propylene glycol. The relative standard deviation for replicate injections determined from the monoester 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 monoesters or diesters in the portion of Propylene Glycol Monolaurate taken by the formula:

$$(100 - D)(r_U / r_s),$$

in which D is the sum of the percentage content of propylene glycol and percentage content of free fatty acids; r_U is the peak response for monoesters or diesters; and r_s is the sum of the responses of the monoesters and diesters peaks. Calculate the percentage content of free fatty acids using the formula:

$$200(A / 561.1),$$

in which A is the acid value.▲*NF24*

BRIEFING

Propylene Glycol Monolaurate. Because there is no existing *NF* monograph for this product, a new monograph, based on the Propylene Glycol Monolaurate monograph in the *European Pharmacopoeia, Fourth Edition,* page 4552, is being proposed.

(EMC: D. Bempong; NL: W. Paul; PSD: C. Okeke)
RTS—41441-1

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Add the following:

▲Propylene Glycol Monolaurate

Dodecanoic acid, monoester with 1,2-propanediol.
Lauric acid, monoester with propane-1,2-diol.

» Propylene Glycol Monolaurate is a mixture of the propylene glycol mono- and di-esters of lauric acid. The requirements for monoester and diester content differ for the two types of Propylene Glycol Monolaurate, as set forth in the accompanying table.

	Content of monoesters (%)		Content of diesters (%)	
	Min.	Max.	Min.	Max.
Type I	45.0	70.0	30.0	55.0
Type II	90.0	—	—	10.0

Packaging and storage—Preserve in well-closed containers, and protect from moisture. No storage requirements specified.

Labeling—Label it to indicate the type (Type I or Type II).

USP Reference standards ⟨11⟩—*USP Propylene Glycol RS. USP Propylene Glycol Monolaurate RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution: 50 mg per mL, in methylene chloride.

Developing solvent solution: a mixture of hexane and ether (30 : 70)

Spray reagent—Prepare a 0.1 mg per mL solution of rhodamine 6G in alcohol.

Procedure—Develop the chromatogram over a path of 15 cm, and dry the plate in a current of air. Spray the plate with *Spray reagent,* and locate the spots on the plate by examination under UV light at a wavelength of 365 nm: the R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the Standard solution.

B: It complies with the requirements of the test for *Fatty acid composition.*

Acid value ⟨401⟩**:** not more than 4.

Iodine value ⟨401⟩**:** not more than 1.

Saponification value ⟨401⟩**:** between 210 to 245 for propylene glycol monolaurate (Type I) and between 200 to 230 for propylene glycol monolaurate (Type II).

Fatty acid composition ⟨401⟩—Propylene Glycol Monolaurate exhibits the following composition profile of fatty acids, determined as directed in the chapter.

Fatty Acids	Carbon-chain Length	Percentage (%)
Caprylic acid	C8	not more than 0.5
Capric acid	C10	not more than 2.0
Lauric acid	C12	not less than 95.0
Myristic acid	C14	not more than 3.0
Palmitic acid	C16	not more than 1.0

Water, *Method Ia* ⟨921⟩**:** not more than 1.0%, using a mixture of methanol and methylene chloride (1 : 1) in place of methanol in the titration vessel.

Total ash ⟨561⟩**:** not more than 0.1%.

Limit of propylene glycol—

Mobile phase—Proceed as directed in the *Assay.*

Propylene glycol standard stock solution—Prepare a solution containing a known concentration of about 4 mg per mL of USP Propylene Glycol RS in tetrahydrofuran.

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Propylene glycol standard solutions—Into four 15-mL flasks, introduce respectively, 0.25 mL, 0.5 mL, 1.0 mL, and 2.5 mL of *Propylene glycol standard stock solution,* and dilute with tetrahydrofuran to 5.0 mL. In a fifth 15-mL flask, introduce 5.0 mL of *Propylene glycol standard stock solution.*

Test solution—Use the *Assay preparation.*

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 40 µL) of the *Propylene glycol standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Prepare a standard curve of peak area versus concentration, in mg per mL, of propylene glycol in the *Propylene glycol standard solutions.* Obtain the concentration, *C,* in mg per mL, of propylene glycol in the *Test solution* from the standard curve. Calculate the percentage of free propylene glycol in the portion of Propylene Glycol Monolaurate taken by the formula:

$$100CV / W,$$

in which V is the final volume of the *Test solution;* and W is the weight, in mg, of Propylene Glycol Monolaurate used to prepare the *Test solution:* not more than 5.0 percent is found for propylene glycol monolaurate (Type I); and not more than 1.0 percent is found for propylene glycol monolaurate (Type II).

Assay—

Mobile phase: tetrahydrofuran.

Assay preparation—Accurately weigh about 200 mg of Propylene Glycol Monolaurate into a 15-mL flask, add 5 mL of tetrahydrofuran, and shake to dissolve.

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 packing L21 (100Å). The flow rate is about 1 mL per minute. The column and detector temperatures are maintained at 40°. [NOTE—Two 7-mm × 30-cm L21 columns may be used in place of one 60-cm column provided system suitability requirements are met.] Chromatograph the *Assay preparation,* and record the peak responses as directed for *Procedure.* The order of elution is diesters, monoesters, and propylene glycol. The relative standard deviation for replicate injections determined from the monoester 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 monoesters or diesters in the portion of Propylene Glycol Monolaurate taken by the formula:

$$(100 - D)(r_U / r_S),$$

in which D is the sum of the percentage content of propylene glycol and percentage content of free fatty acids; r_U is the peak response for monoesters or diesters; and r_S is the sum of the responses of the monoesters and diesters peaks. Calculate the percentage content of free fatty acids using the formula:

$$200(A / 561.1),$$

in which A is the acid value.▲*NF24*

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**1**⟩ **Injections,** *USP 28* page 2201 and page 707 of *PF* 29(3) [May–June 2003]. The Food and Drug Administration (FDA) is amending its regulations to change the labeling requirements for aluminum in large- and small-volume parenterals and pharmacy bulk packages used in total parenteral nutrition (TPN). The Parenteral Products Industrial Expert Committee has decided to adopt these labeling requirements with the addition that the small-volume injections (SVIs) such as lock flush solutions that are used in the administration of TPN products also meet these requirements. The Committee believes that the quantity of parenterally administered aluminum contributed by lock flush solutions used during TPN therapy is as serious a concern as the aluminum from the SVIs used in the preparation of TPN products for the same reasons expressed in the Background information of the originally published Final Rule notice [*Federal Register,* 65 (17): 4103–4111 (Jan. 26) 2000].

The sections *Foreign Matter* and *Particulate Matter* have been combined and rewritten so that the "essentially free" terminology, which is currently in *Particulate Matter in Injections* ⟨788⟩ and only in *Constituted Solutions* in this chapter, will apply to all injectables. In this manner all articles that are intended for parenteral administration shall be inspected to the extent possible for presence of observable foreign and particulate matter in its contents.

(PPI: J. Kelly) RTS—41973-2

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Change to read:

LABELS AND LABELING

Labeling—[NOTE—See definitions of "label" and "labeling" under *Labeling* in the section *Preservation, Packaging, Storage, and Labeling* of the *General Notices and Requirements.*]

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

~~Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition~~

~~(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (µg/L).~~

~~(b) The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per liter. This information must be contained in the "Precautions" section of the labeling of all large volume parenterals used in TPN therapy.~~

~~(c) The maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: "Contains no more than ___ µg of aluminum per liter." The immediate container label of all~~

~~SVPs and PBPs that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than _____ µg per liter." This maximum level of aluminum must be stated as the highest of the following:~~

~~(1) The highest level for the batches produced during the last 3 years;~~

~~(2) The highest level for the latest five batches, or~~

~~(3) The maximum historical level, but only until completion of production of the first five batches after January 26, 2001.~~

~~(d) The package insert for all LVPs, all SVPs, and PBPs used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state the following:~~

~~WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum.~~

~~Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.~~ ■ ~~as (USP28)~~

▲Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy

(a) The aluminum content of LVIs used in TPN therapy must not exceed 25 µg per L.

(b) The package insert of LVIs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVIs used in TPN therapy.

(c) If the maximum amount of aluminum in SVIs and PBPs is 25 µg per L or less, instead of stating the exact amount of aluminum that each may contain, as in paragraph (d), the immediate container label for SVIs and PBPs used in the preparation or in the administration of TPN injections (with exceptions as noted below) and injectable emulsions may state: "Contains no more than 25 µg/L of aluminum". If the SVI or PBP is a lyophilized powder, the immediate container label may state the following; if the SVI or PBP is a lyophilized powder used in the preparation of TPN injections and injectable emulsions, the immediate container label must state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L".

(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVIs and PBPs used in the preparation or the administration of TPN injections and injectable emulsions. The alumi-

num content must be stated as follows: "Contains no more than __ µg/L of aluminum''. This maximum amount of aluminum may be stated as the highest one of the following three levels:

1. The highest level for the batches produced during the last three years
2. The highest level for the latest five batches
3. The maximum level in terms of historical levels, but only until completion of production of the first five batches after the effective date of July 26, 2004

The package insert for all LVIs, SVIs, and PBPs used in the preparation or administration of TPN products must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling and must state the following: "WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products and of the lock-flush solutions used in their administration."▲*USP29*

Change to read:

~~**FOREIGN MATTER AND PARTICLES**~~

▲FOREIGN AND PARTICULATE MATTER▲*USP29*

~~**Foreign Matter**~~

~~Every care should be exercised in the preparation of all products intended for injection to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents shows evidence of contamination with visible foreign material be rejected.~~

~~**Particulate Matter**~~

~~All large-volume Injections for single-dose infusion, and those small-volume Injections for which the monographs specify such requirements, are subject to the particulate matter limits set forth under *Particulate Matter in Injections* ⟨788⟩. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 ml or less if the individual monograph includes a test for *Particulate Matter;* it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter*.~~

▲All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* ⟨788⟩ and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed "visible particulates") in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container whose contents shows evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container-closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume Injections for single-dose infusion and small-volume Injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in *Particulate Matter In Injections* ⟨788⟩, unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for *Particulate Matter* ⟨788⟩; it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections administered exclusively by the intramuscular or subcutaneous route or packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter* ⟨788⟩.▲*USP29*

BRIEFING

⟨**11**⟩ **USP Reference Standards,** *USP 28* page 2204, the *Fifth Interim Revision Announcement* on page 1559 of *PF* 30(5) [Sept.–Oct. 2004], *Sixth Interim Revision Announcement* on page 1965 of *PF* 30(6) [Nov.–Dec. 2004], *First Interim Revision Announcement* on page 33 of *PF* 31(1) [Jan.–Feb. 2005], page 793 of *PF* 26(3) [May–June 2000], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 3071 of *PF* 27(5) [Sept.–Oct. 2001], 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 710 of *PF* 29(3) [May–June 2003], page 1137 of *PF* 29(4) [July–Aug. 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 211 of *PF* 30(1) [Jan.–Feb. 2004], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 998 of *PF* 30(3) [May–June 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], and page 99 of *PF* 31(1) [Jan.–Feb. 2005].

(HDQ) RTS—37475-1; 37658-1; 41266-3; 41441-1; 41442-1; 41493-4; 41757-1; 42069-1; 41493-4; 42051-1; 42216-1

Add the following:

▲**USP Ademetionine Disulfate Tosylate RS**—Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light, and store in a refrigerator.▲*USP29*

Delete the following:

~~▲USP Bupropion Hydrochloride Related Compound D RS [2-(*tert*-butylamino)propiophenone hydrochloride] ($C_{13}H_{19}NO \cdot HCl$ ✧ 241.76)—Do not dry. Store at 5°.▲*USP29*~~

Delete the following:

~~▲USP Bupropion Hydrochloride Related Compound E RS [1-(3-chlorophenyl)-1,2-propandione] ($C_9H_7O_2Cl$ ✧ 182.61)—Do not dry. Store at 5°.▲*USP29*~~

Add the following:

▲**USP 2-(Dimethylaminomethyl)-1-cyclohexanone Hydrochloride RS** ($C_9H_{17}NO \cdot HCl$ ✧ 191.7)—[To come.]▲*USP29*

Add the following:

▲**USP Fish Oil RS**—[To come.]▲*USP29*

Add the following:

▲**USP Goserelin RS**—[To come.]▲*USP29*

Add the following:

▲**USP Goserelin Related Compound A RS [**4-D-Ser-goserelin**]**—[To come.]▲*USP29*

Add the following:

▲**USP Goserelin Validation Mixture RS**—[To come.]▲*USP29*

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Add the following:

▲**USP Neotame RS**—[To come.]▲*USP29*

Add the following:

▲**USP Neotame Related Compound A RS [***N*-[3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine**]**—[To come.]▲*USP29*

Add the following:

▲**USP Omega-3 Ethyl Esters RS**—[To come.]▲*USP29*

Add the following:

▲**USP Oxandrolone Related Compound C RS [**anhydrooxandrolone (17,17-dimethyl-2-oxa-18-nor-5α-androstan-3-one)**]**—[To come.]▲*USP29*

Add the following:

▲**USP Propylene Glycol Dilaurate RS**—[To come.]▲*USP29*

Add the following:

▲**USP Propylene Glycol Monolaurate RS**—[To come.]▲*USP29*

Add the following:

▲**USP Tazobactam RS**—[To come.]▲*USP29*

Add the following:

▲**USP Tizanidine RS**—[To come.]▲*USP29*

Add the following:

▲**USP Tizanidine Related Compound A RS [**4-amino-5-chloro-2,1,3-benzothiadiazole**]** ($C_6H_4ClN_3S$ ✧ 185.63)—[To come.]▲*USP29*

Add the following:

▲**USP Tizanidine Related Compound B RS [***N*-acetyltizanidine**]** ($C_{11}H_{10}ClN_5OS$ ✧ 295.75)—[To come.]▲*USP29*

Add the following:

▲**USP Tizanidine Related Compound C RS [**1-acetylimidazolidine-2-thione**]** ($C_5H_8N_2OS$ ✧ 144.20)—[To come.]▲*USP29*

Add the following:

▲**USP Tramadol Hydrochloride RS**—[To come.]▲*USP29*

Add the following:

▲**USP Tramadol Related Compound A RS [***RS,SR*-1-(3-methoxyphenyl)-2-(dimethylaminomethyl-cyclohexanol hydrochloride**]**—[To come.]▲*USP29*

Apparatus for Tests and Assays

BRIEFING

⟨**41**⟩ **Weights and Balances,** *USP 28* page 2242 and page 999 of *PF* 30(3) [May–June 2004]. On the basis of comments received, it is proposed to include reference to OIML R111. OIML R111 is the international standard for the design, manufacture, and testing of mass artifacts, while ASTM E617-97 is the U.S. national standard for weights. ASTM E617-97 acknowledges OIML R111 as Appendix X4 with the intent that upon completion of the revision of R111 the revised document would become an Appendix of E617. This change would provide harmonization for international users of the *USP*.

It is also proposed to add sections to the chapter to address the need to verify linearity and span accuracy. It is also recommended that two significant digits, 0.10%, be used in the definition of the expanded relative uncertainty. The multiplier '3' is based on a desired number of standard deviations providing a specified confidence in the result. Adding the explanatory text defining the confidence interval clarifies the reason for using the specified multiplier. To be truly meaningful, the measurement uncertainty of a weighing process must be determined at the time and under the conditions of routine mass measurements. Standard deviation values based on data obtained over a short time period, as described by the "suitability test", reflect only the performance of the weighing system under the conditions present at that time and when used by that individual. A standard deviation calculated from data obtained over a relatively long time period by multiple users of the weighing system, under normal but varying conditions, will reflect the true performance of the weighing system. The resulting measurement uncertainty is based on real measurement data that accounts for all typically encountered measurement error sources that may affect the reported measurement result.

Use of *Equation 10* to calculate the minimum permissible load, m_{min}, for a balance will provide a reasonable estimate of the minimum load for which the actual balance performance will have an error less than the permitted 0.10 % of load. *Equation 5* provides an initial value useful for placing a weighing system in service, based on short term and limited information. The result of *Equation 10* is based on long-term measured weighing system performance and provides the user with significantly increased confidence in the measurement result due to the increased numbers of measurements on which it is based.

(PA4: H. Pappa) RTS—41768-1; 41811-1; 41940-1; 42013-1

Change to read:

~~The intent of this section is to bring the requirements for weights into conformity with American National Standard ANSI/ASTM E617, "Laboratory Weights and Precision Mass Standards." This standard is incorporated by reference and should be consulted for full descriptions and information on the tolerances and construction of weights.[1]~~

~~Pharmacopeial tests and assays require balances that vary in capacity, sensitivity, and reproducibility. Unless otherwise specified, when substances are to be "accurately weighed" for *Assay* the weighing is to be performed with a weighing device whose measurement uncertainty (random plus systematic error) does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001. Unless otherwise specified, for titrimetric limits tests, the weighing shall be performed to provide the number of significant figures in the weight of the analyte that corresponds to the number of significant figures in the concentration of the titrant.~~

~~The class designations below are in order of increasing tolerances.~~

~~Class 1.1 weights are used for calibration of low capacity, high-sensitivity balances. They are available in various denominations from 1 to 500 mg. The tolerance for any denomination in this class is 5 µg. They are recommended for calibration of balances using optical or electrical methods for accurately weighing quantities below 20 mg.~~

~~Class 1 weights are designated as high precision standards for calibration. They may be used for weighing accurately quantities below 20 mg. (For weights of 10 g or less, the requirements of class 1 are met by *USP XXI* class M.)~~

~~Class 2 weights are used as working standards for calibration, built-in weights for analytical balances, and laboratory weights for routine analytical work. (The requirements of class 2 are met by *USP XXI* class S.)[2]~~

~~Class 3 and class 4 weights are used with moderate precision laboratory balances. (Class 3 requirements are met by *USP XXI* class S 1; class 4 requirements are met by *USP XXI* class P.)[2]~~

~~A weight class is chosen so that the tolerance of the weights used does not exceed 0.1% of the amount weighed. Generally, class 2 may be used for quantities greater than 20 mg, class 3 for quantities of greater than 50 mg, and class 4 for quantities of greater than 100 mg. Weights should be calibrated periodically, preferably against an absolute standard weight.~~

~~[1] Copies of ASTM Standard E 617-81 (Reapproved 1985) may be obtained from the American Society for Testing and Materials, 1916 Race Street, Philadelphia, PA 19103.~~

~~[2] Note that the designations S and P no longer designate weight classes but rather weight grades, that is, design limitations such as range of density of materials, surface area, surface finish, corrosion resistance, and hardness.~~

▲INTRODUCTION

Measurement processes are generally subject to a wide variety of influences. Weighing is no exception and may get distorted by many factors that introduce bias and uncertainty into the results. The distortions may be caused by properties of the weighing object, the balance, the environment, and the procedure used to weigh the object.

Influences originating from the balance, itself, are manifold. They include effects introduced by the following properties of the balance: quantized digital display, limited capability to repeat, nonlinear characteristic, sensitivity to eccentric loading, deviation of sensitivity from the correct value, and temperature dependence. Among the factors that affect the weighing object, the most prominent is buoyancy, which is caused by the fact that weighings are usually being carried out in air instead of empty space (i.e., a vacuum). Determination of the weight of objects with large surface areas is also affected by air drafts (even in the presence of draft shields), by electrostatic charge buildup (e.g., glass, plastic, or other electrically insulating materials), and by magnetic forces (e.g., stirring magnets or magnetically permeable objects). Additionally, materials that absorb moisture from, or dissipate moisture to, the surrounding environment may result in significant measurement errors.

Ambient conditions such as air temperature, humidity, pressure, and air velocity will also have an effect on the weighing object and the balance. In addition, effects caused by vibration, inclination, or other conditions may also be present.

In the following sections the requirements for weights and balances are described.

WEIGHTS

ASTM standard E617, "Standard Specification for Laboratory Weights and Precision Mass Standards", ~~is~~ OIML recommendation R111, "Weights of Classes E1, E2, F1, F2, M1, M1-2, M2, M2-3, and M3" and NIST Handbook 105-1, "Specifications and Tolerances for Field Standard Weights (NIST Class F)", are incorporated by reference and ~~is~~ are to be consulted for full descriptions and information on the tolerances and construction of weights.[1]

Weights are periodically calibrated against standard masses. The mass of each weight thus determined is referred to as its calibration mass value, and the difference between the nominal mass value and the calibration mass value is referred to as its calibration error.

When weights are used with beam balances to weigh materials, the weight class is chosen so that the tolerances of the weights do not exceed ~~0.1%~~ 0.10% of the net amount weighed. If the weights meet the tolerances of the corresponding ~~ASTM class (currently 8 classes, numbered 0–7)~~ ASTM or OIML class, corrections for calibration errors are not required. If, however, weights are used to calibrate beam or electronic balances, different criteria apply.

The class designations below are listed in order of increasing tolerances.

- ~~*Class 0* and *Class 1* weights are designated as high-precision standards for calibration. Use of *Class 0* and *Class 1* weights requires careful control of relative humidity and temperature and accurate monitoring of barometric pressure, as specified by the weight manufacturer.~~
- ~~*Class 1* and *Class 2* weights may be used as laboratory weights for routine analytical work. Weights in *Class 0* through *Class 3* are available in denominations from 1 mg to 50 kg, and their tolerances vary with class and nominal values.~~
- ~~*Class 4*, *Class 5*, and *Class 6* weights may be used with moderate-precision balances, trip balances, dial scales, and platform scales; they are available in denominations from 1 mg to 5000 kg, and their tolerances vary with nominal values.~~
- ~~*Class 7* weights are used in rough weighing operations.~~

- Weights complying with the requirements of ASTM Classes 0 and 1, and OIML Classes E1 and E2 are designated as high-precision standards for calibration. Use of Class 0, 1, E1, and E2 weights requires careful control of relative humidity and temperature and accurate monitoring of barometric pressure as well as special handling to prevent contamination.
- Weights complying with the requirements of ASTM Classes 1, 2, and 3, and OIML Classes E2 and F1 may be used as laboratory weights for routine analytical work. Weights in Classes 1 through 3, and E2 and F1 are available in denominations from 1 mg to 50 kg, and their tolerances vary with class and nominal values. Special handling is required to prevent contamination.
- Weights complying with the requirements of ASTM Classes 4, 5, and 6 and OIML Classes F1, F2, and M1 may be used with moderate-precision balances, trip balances, dial scales, and platform scales; they are available in denominations from 1 mg to 5000 kg, and their tolerances vary with nominal values.

[1] Copies of ASTM standard E617 may be obtained from ASTM, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959 www.astm.org. Copies of OIML R111 may be obtained from OIML, 11 Rue Turgot–75009 Paris, France, www.oiml.org. Copies of NIST Handbook 105-1 may be obtained from NIST Weights and Measures Division, 100 Bureau Drive, Mail Stop 2600, Gaithersburg, MD 20899, www.nist.gov/labmetrology, or E-mail: owm@nist.gov.

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- Weights complying with NIST Handbook 105-1 may be required for calibration of weighing devices complying with NIST Handbook 44, *Specifications, Tolerances, and Other Technical Requirements for Weighing and Measuring Devices,* such as Classes III or IIIL that are used for commercial purposes. NIST Class F weights are available in denominations from 1 mg to 500 kg and 0.001 lb to 10,000 lb, and their tolerances vary with nominal values.
- Weights complying with the requirements of ASTM Class 7 and OIML Classes M2 and M3 are used in rough weighing operations.

BALANCES

Pharmacopeial procedures require balances that vary in capacity, readability, and repeatability.

As stated in the *Introduction,* there are a number of factors that influence the use of balances. These factors must be controlled in order to obtain accurate measurements. To ensure that balances will provide the performances expected of USP weight measurements, balances must be calibrated. There are three characteristics that are to be verified: 1) span accuracy, 2) linearity, and 3) repeatability. Span accuracy and linearity tests are to be performed during routine calibrations of the balance and are typically performed by a calibration organization. The repeatability test is used to determine the suitability of a weighing device initially and at established intervals thereafter. The repeatability test may be performed by the user or by a calibration organization.

There are two methods for evaluating the accuracy (departure from nominal value) and linearity of the balance. In the first method, the accuracy and linearity are evaluated together (*Span Accuracy and Linearity Test, Combined*). In the second method, they are evaluated independently (*Span Accuracy and Linearity Test, Independent*).

Span Accuracy and Linearity Test, Combined—Tests of accuracy and linearity may be performed together because linearity is often considered to be a component of the overall accuracy. Other accuracy components are offset (zero uncertainty) and span (sensitivity) uncertainty. Because accuracy represents the proximity to true value, nonlinearity is a point-by-point measure of accuracy if the zero point and the full-scale calibration point have been set true. Test points may be selected in an arithmetic (e.g., 0, 20, 40, 60, 80, 100) or near geometric series (e.g., 1, 2, 5, 10, 20, 50, 100). At least five different test points (including zero) are chosen, and all test weights used are calibrated.

Span Accuracy and Linearity Test, Independent—To evaluate span errors and nonlinearity independently, the following method may be used. Nonlinearity can be determined when the same test weight is weighed on top of different amounts of tare. A test weight of about 20% to 25% of the span of the balance is first weighed without a tare, then together with tare weights of approximately the same, double, and triple the test weight (and quadruple if the test weight is about 20% of the span), respectively, setting the balance to zero each time before adding the test weight to the tare. Neither the test weights nor the tare weights need to be calibrated. *Span Accuracy,* i.e., calibration error or span error, is tested by weighing a calibrated standard mass at one point in the upper 30% of the balance range. The advantages of the independent approach are that only one calibrated weight is required, and it is at a mass where weight tolerances are favorable.

Uncertainty, Repeatability, and Minimum Weight—When substances are to be "accurately weighed", weighings have to be performed with an expanded relative uncertainty, U_{rel}, equal to or smaller than ~~0.1%~~ 0.10%, observing a

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coverage factor, *k,* of 3 for a confidence interval of approximately 99.73%. The expanded relative uncertainty, U_{rel}, is thus given by the following expression:

$$U_{rel} = ku_{rel} = 3u_{rel}, \qquad (1)$$

in which the relative standard uncertainty, u_{rel}, is given by the formula:

$$u_{rel} = u/m, \qquad (2)$$

in which u is the (absolute) standard uncertainty of the weighing; and m is the weighed sample (or net) mass to which this uncertainty applies. From *Equation 1* and *Equation 2,* we get the following:

$$U_{rel} = ku/m. \qquad (3)$$

The smallest possible amount of mass that meets the aforementioned requirement is known as the ''minimum weight'', which can be obtained from the following formula:

~~$m_{min} \geq (k/U_{rel})u = (3/0.1\%)u = 3000u$ (4)~~

$$m_{min} \geq (k/U_{rel})u = (3/0.10\%)u = 3000u. \qquad (4)$$

For cases in which a small mass (compared to the maximum capacity of the balance) is considered, it is generally sufficient to represent the standard uncertainty, *u,* of the weighing by its repeatability, defined here as the standard deviation, S_{RP}, of not fewer than ten replicate weighings. Other contributors to uncertainty (from sources such as linearity deviation, eccentric load deviation, or sensitivity offset) are much smaller and thus may be neglected. This leads to a simple expression for m_{min}, whereby the minimal sample mass depends only on one property of the weighing, namely its repeatability:

$$m_{min} \geq (k/U_{rel})S_{RP}, \qquad (5)$$

in which S_{RP} represents the standard deviation of not fewer than ten replicate weighings obtained from the individual net readings, R_i, as follows:

$$S_{RP} = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(R_i - \overline{R})^2}, \qquad (6)$$

in which

$$\overline{R} = \frac{1}{n}\sum_{i=1}^{n} R_i. \qquad (7)$$

The test weighings must be performed with a weighing setup under conditions as similar as possible to those expected for later use, including the following: configuration of the balance, type of weighing object (sample and/or container), weighing procedure, environmental conditions, and the site of use. ~~If weights are used to simulate the sample mass, they need not be calibrated.~~ Weights used for this short-term repeatability test need not be calibrated.

As the standard deviation, S_{RP}, is reduced to a value equal ~~or even~~ to or less than the readability, *d,* of a digital balance, ~~then~~ the influence of the necessary rounding between two indication steps on the weighing value becomes predominant. Similarly, the standard deviation estimated from repeated weighings is influenced by the average weighing value ~~and it may accidentally~~ and, as a result of balance

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resolution and the small number of readings, may vanish altogether, i.e., have a value of zero. ~~To prevent this, a replacement~~ When this situation occurs, a minimum value for the standard uncertainty of no less than $0.4d$ must be observed, as shown below:

$$S_{RP} \geq 0.4d. \qquad (8)$$

~~Thus~~ Therefore the minimal weight, m_{min}, ~~is~~ will be greater than $3000S_{RP}$ or greater than $1200d$, whichever is larger.

This suitability test differs from routine calibrations of the balance. It is used to determine the suitability of a weighing device initially and at established intervals thereafter ~~Measurement uncertainty may be determined as part of the balance maintenance and calibration, and need not be repeated with every weighing.~~ and forms the baseline for continued evaluation of balance performance. The frequency of testing, as well as the measurement conditions, are established by the balance user and form a part of the laboratory standard operating procedures. Routine measurement uncertainty is determined as described in the following paragraphs.

The uncertainty of routine measurements is based on data accumulated over time through the use of stable check standard artifacts as part of routine mass measurement processes, using a minimum of 32 values, subject to the same measurement influences as the routine measurements. Check standards are selected to approximate the typical test loads measured during routine mass measurements and will be used at intervals established using generally accepted measurement assurance techniques[2] and documented in the user's standard operating procedures. Each measured value of the check standard is immediately entered in a measurement assurance control chart and evaluated for appropriateness. An appropriate measurement result is one that is within three standard deviations, $3u$, of either a reference value for the artifact or the median of the recorded values when no reference value is available. The uncertainty of routine mass measurement results, U, is calculated by the following equation:

$$U = 3\sqrt{u^2 + (0.58t_b)^2}, \qquad (9)$$

where t_b is the calibration tolerance of the balance at the test load measured; 0.58 is a multiplier converting the balance tolerance, t_b, to a value equivalent to one standard deviation; u is the standard deviation of the check standard values from the control chart; and $k = 3$ provides a confidence interval of 99.73% for the measurement result. The value of U may be used as an alternative method for calculating m_{min}, by using the formula:

$$m_{\min} > \frac{U}{0.001}. \qquad (10)$$

The result of this equation is typically larger than the value calculated in *Equation 5*; however, this result is based on actual long-term measurement results and is most representative of the true weighing system performance.▲*USP29*

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[2] NISTIR 6969, Selected Laboratory and Measurement Practices and Procedures, to Support Basic Mass Calibrations, SOP 30.

Chemical Tests and Assays

OTHER TESTS AND ASSAYS

BRIEFING

⟨**345**⟩ **Assay for Citric Acid/Citrate and Phosphate.** This new general chapter provides an ion chromatographic procedure for the assay of citric acid/citrate and phosphate. The procedure is based on analyses performed using a liquid chromatograph equipped with an anion trap column (ATC), an AG11 brand of L61 guard column, an IonPac AS11 brand of L61 analytical column, and an electrochemical detector equipped with ASRS-ULTRA II for suppressed conductivity detection. Typical retention times are about 4 minutes for phosphate and 6 minutes for citrate.

(PA2: D. Bempong) RTS—42134-1

Add the following:

▲⟨345⟩ ASSAY FOR CITRIC ACID/ CITRATE AND PHOSPHATE

The following ion chromatographic general procedure is provided for the determination of citric acid/citrate and phosphate in compendial articles, when specified in the individual monographs. Identification tests for citrate and phosphate are provided separately under USP general chapter *Identification Tests—General* ⟨191⟩. The procedure for preparation of the *Standard Preparations* used for the assay depends on whether or not citrate and phosphate are being assayed concomitantly, as indicated below.

USP Reference Standards ⟨11⟩—*USP Citric Acid RS.*

Mobile Phase—Transfer an appropriate volume of water (resistivity not less than 18 megohm-cm) to a suitable container, and degas with helium for not less than 20 minutes. Add an appropriate volume of 50% (w/w) carbonate-free sodium hydroxide or potassium hydroxide to obtain a 20 mM sodium hydroxide or potassium hydroxide solution. Alternatively, a 20 mM sodium hydroxide or potassium hydroxide eluant can be generated electrolytically using an automatic eluant generator. [NOTE—Protect the *Mobile Phase* from atmospheric carbon dioxide.]

Standard Preparations—Use *Standard Preparation 1* for an assay for citric acid/citrate only. Use *Standard Preparation 2* when a concomitant assay for citrate and phosphate is intended.

Standard Preparation 1—Dissolve USP Citric Acid RS in freshly prepared 1 mM sodium hydroxide to obtain a solution having a known concentration of about 20 µg per mL of citrate $(C_6H_5O_7)^{-3}$.

Standard Preparation 2—Dissolve USP Citric Acid RS and monobasic sodium phosphate in freshly prepared 1 mM sodium hydroxide to obtain a solution having known concentrations of about 20 µg per mL and 12 µg per mL of citrate and phosphate $(PO_4)^{-3}$, respectively.

Assay Preparation for Citric Acid/Citrate Assay—Unless stated otherwise in the monograph, dissolve an appropriate quantity of a solid dosage form in freshly prepared 1 mM sodium hydroxide to obtain a solution containing about 20 µg per mL of citrate. If the dosage form is a liquid formulation, dilute with water, and add a freshly prepared sodium hydroxide solution to obtain a solution containing about 20 µg per mL of citrate in 1 mM sodium hydroxide.

Assay Preparation for Phosphate Assay—Unless stated otherwise in the monograph, dissolve an appropriate quantity of a solid dosage form in freshly prepared 1 mM sodium hydroxide to obtain a solution containing about 12 µg per mL of phosphate. If the dosage form is a liquid formulation, dilute with water, and add a freshly prepared sodium hydroxide solution to obtain a solution containing about 12 µg per mL of phosphate in 1 mM sodium hydroxide.

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Chromatographic System (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a suitable anion trap column; a 4-mm × 50-mm guard column and a 4-mm × 250-mm analytical column, both packed with L61 packing; and an electrochemical detector with suppressed conductivity detection using either a micromembrane anion autosuppressor or a suitable chemical suppression system. All columns are maintained at 30° and eluted at a flow rate of 2 mL per minute. [NOTE—An anion trap column designed to remove trace anion contaminants in the *Mobile Phase* should be added to the column assembly before the injector.] Chromatograph *Standard Preparation 1* or *Standard Preparation 2,* as appropriate, and record the peak area responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation of the peak areas for citrate (and phosphate where appropriate), for six replicate injections of *Standard Preparation 1* or *Standard Preparation 2,* is not more than 1.5%.

Procedure—Separately inject 10 µL each of the appropriate *Standard Preparation* and *Assay Preparation* into the chromatograph, record the chromatograms, and measure the peak areas for citrate and phosphate, as appropriate. Determine the concentrations of citrate or phosphate in the portion of *Assay Preparation* taken by the formula:

$$C_S(r_U / r_S),$$

in which C_S is the concentration of citrate or phosphate, in µg per mL, in the appropriate *Standard Preparation;* and r_U and r_S are the peak areas of citrate or phosphate obtained from the *Assay Preparation* and the *Standard Preparation,* respectively.▲*USP29*

Physical Tests and Determinations

BRIEFING

⟨**841**⟩ **Specific Gravity,** *USP 28* page 2492. It is proposed to add a new method for determination of specific gravity. This method is based on the use of the oscillating transducer density meter and is designated as *Method II.* The official method using pycnometers is designated as *Method I,* which is to be used unless otherwise directed in the individual monograph. Editorial style changes have also been made.

Manufacturers interested in incorporating *Method II* in compendial monographs are encouraged to submit appropriate requests for revision with supporting documentation.

(PA4: E. Gonikberg) RTS—40825-1

Change to read:

Unless otherwise stated in the individual monograph, the specific gravity determination is applicable only to liquids, and, unless otherwise stated, is based on the ratio of the weight of a ~~substance~~

▲liquid▲*USP29*
in air at 25° to that of an equal volume of water at the same temperature. Where a temperature is specified in the individual monograph, the specific gravity is the ratio of the weight of the ~~substance~~

▲liquid▲*USP29*
in air at the specified temperature to that of an equal volume of water at the same temperature. When the substance is a solid at 25°, determine the specific gravity

▲of the melted material▲*USP29*
at the temperature directed in the individual monograph, and refer to water at 25°.

▲Unless otherwise stated in the individual monograph, the density is defined as the mass of a unit volume of the substance at 25°, expressed in kilograms per cubic meter or grams per cubic centimeter ($1\ kg/m^{-3} = 10^{-3}\ g/cm^{-3}$).

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Unless otherwise directed in the individual monograph, use *Method I.*▲*USP29*

Change to read:

▲METHOD I▲*USP29*

Procedure—Select a scrupulously clean, dry pycnometer that previously has been calibrated by determining its weight and the weight of recently boiled water contained in it at 25°. Adjust the temperature of the ~~substance~~

▲liquid▲*USP29*
to about 20°, and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25°, remove any excess ~~of the substance,~~

▲liquid,▲*USP29*
and weigh.

▲When the monograph specifies a temperature different from 25°, filled pycnometers must be brought to the temperature of the balance before they are weighed.▲*USP29*
Subtract the tare weight of the pycnometer from the filled weight. ~~of the pycnometer.~~

▲▲*USP29*
The specific gravity of the ~~substance~~

▲liquid▲*USP29*
is the quotient obtained by dividing the weight of the ~~substance~~

▲liquid▲*USP29*
contained in the pycnometer by the weight of water contained

▲in it,▲*USP29*
both determined at 25°, unless otherwise directed in the individual monograph.

Add the following:

▲METHOD II

The procedure includes the use of the *Oscillating transducer density meter.* The apparatus consists of the following:

— a U-shaped tube, usually of borosilicate glass, which contains the liquid to be examined;
— a magneto-electrical or piezo-electrical excitation system that causes the tube to oscillate as a cantilever oscillator at a characteristic frequency depending on the density of the liquid to be examined;
— a means of measuring the oscillation period *(T),* which may be converted by the apparatus to give a direct reading of density or used to calculate density by using the constants *A* and *B* described below; and
— a means to measure and/or control the temperature of the oscillating transducer containing the liquid to be tested.

The oscillation period is a function of the spring constant *(c)* and the mass of the system:

$$T^2 = \left(\frac{M}{c} + \frac{\rho \times V}{c} \right) \times 4\pi^2$$

where ρ is the density of the liquid to be tested, M is the mass of the tube, and V is the volume of the filled tube.

Introduction of two constants $A = c/(4\pi^2 \times V)$ and $B = M/V$, leads to the classical equation for the oscillating transducer:

$$\rho = A \times T^2 - B.$$

The specific gravity of the liquid is given by the formula:

$$\rho_{(L)} / \rho_{(W)},$$

where $\rho_{(L)}$ and $\rho_{(W)}$ are the densities of the liquid and water, respectively, both determined at 25°, unless otherwise directed in the individual monograph.

Calibration—The constants A and B are determined by operating the instrument with the U-tube filled with two different samples of known density (e.g., degassed water and air). Perform the control measurements daily using degassed water: the results displayed for the control measurement using degassed water do not deviate from the reference value ($\rho_{25} = 0.997043$ g/cm^{-3}) by more than its specified error. Precision is a function of the repeatability and stability of the oscillator frequency. Density meters are able to achieve

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measurements with an error on the order of 1×10^{-3}g/cm^{-3} to 1×10^{-5}g/cm^{-3} and a repeatability of 1×10^{-4}g/cm^{-3} to 1×10^{-6}g/cm^{-3}. For example, an instrument specified to $\pm 1 \times 10^{-4}$g/cm^{-3} must display 0.9970 $\pm$ 0.0001 g/cm^{-3} in order to be suitable for further measurement, otherwise a re-adjustment is necessary. Calibration with certified reference materials should be carried out regularly.

Procedure—Using the manufacturer's instructions, perform the measurements using the same procedure as for *Calibration.* If necessary, equilibrate the liquid to be examined at 25° before introduction into the tube to avoid the formation of bubbles and to reduce the time required for measurement. Factors affecting accuracy include the following:

— temperature uniformity throughout the tube,
— nonlinearity over a range of density,
— parasitic resonant effects, and
— viscosity, if the oscillating transducer density meters used do not provide automatic compensation of sample viscosity influence.▲*USP29*

BRIEFING

⟨**921**⟩ **Water Determination,** *USP 28* page 2510. On the basis of comments received, it is proposed to revise the *Test Preparation* and *Standardization of the Reagent* sections under *Method Ia*. For a sample with a trace amount of water, the sensitivity of the method can be improved by using a small buret and a reagent with a low water equivalency factor. A formula to estimate the sample size is also included. Additional recommendations are added for standardization of the *Reagent* used for determination of the trace amount of water.

(PA4: H. Pappa) RTS—41925-1

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 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~~ ▲2 to 250 mg of water. The amount of water depends on the water equivalency factor of the *Reagent* and on the method of endpoint determination. In most cases, the minimum amount of specimen, in mg, can be estimated using the formula:

$$FCV / KF,$$

in which F is the water equivalency factor of the *Reagent,* in mg per mL; C is the used volume, in percent, of the capacity of the buret; V is the buret volume, in mL; and KF is the limit or reasonable expected water content in the sample, in percent. C is between 30% and 100% for manual titration, and between 10% and 100% for the instrumental method endpoint determination.▲*USP29*

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 fewer than 4 capsules.

Where the specimen under test is tablets, use powder from not fewer 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~~ ▲it is preferable to use *Reagent* with a water equivalency factor of not more than 2.0. Sodium▲*USP29* tartrate may be used as a convenient water reference substance. Quickly add ~~150 to 350 mg~~ ▲75 to 125 mg▲*USP29* 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.

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 con-

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tent 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.

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.

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1065**⟩ **Ion Chromatography.** Because there is no *USP* general information chapter for this subject, a new chapter describing apparatus configurations and recommended procedures for this technique is being proposed.

(PA2: H. Pappa) RTS—41923-1

Add the following:

▲⟨1065⟩ ION CHROMATOGRAPHY

INTRODUCTION

Ion chromatography (IC) is a high-performance liquid chromatography (HPLC) instrumental technique used in *USP* test procedures such as identification and assay tests to measure inorganic anions and cations, organic acids, carbohydrates, sugar alcohols, aminoglycosides, amino acids, proteins, glycoproteins, and potentially other analytes.

In-Process Revision

As dictated by the nature of the analyte, IC has been applied to all aspects of the manufacturing and disposition of pharmaceutical products, including characterization of active ingredients, excipients, degradation products, impurities, and process streams. The following sample types are among those that have been analyzed: raw materials, intermediates (including media and culture broths), bulk active ingredients, diluents, formulated products, production equipment cleaning solutions, and waste streams. The technique is especially valuable for ionic or ionizable (in the mobile phase) analytes that have little or no native UV absorbance. The ability to couple the ion-exchange separation with numerous detection strategies, e.g., pulsed amperometric detection (PAD), expands IC applications to instances where analyte-specific detection strategies can provide the required degree of sensitivity or specificity. Utilization of such strategies allows IC applications to be implemented on appropriately configured HPLC systems. Additionally, ion-exclusion separations and pulsed amperometric detection expand the range of application of IC to aliphatic organic acids as well as to nonionic analytes of significant pharmaceutical interest including alcohols, alditols, carbohydrates, and amino acids. The wide dynamic range of the methodology makes it applicable for the quantification of trace contaminants as well as major product components.

Because IC typically uses dilute acids, alkalis, or salt solutions as the mobile phase, and does not use an organic solvent, IC does not require the purchase of costly organic solvents and hazardous disposal of the waste effluent. The effluent can be disposed of after appropriate neutralization (to ~pH 7) and, when necessary, after dilution with water.

IC allows separation using ion exchange, ion exclusion, or ion-pair approaches. IC separations are based on differences in charge density of the analyte species, which in turn depend on the valence and size of the individual ionic species to be measured. Separations are also performed on the basis of differences in the hydrophobic character of the ionic species. IC is typically performed at ambient temperature. As with other forms of HPLC, IC separations are based on varying capacity factors and typically follow the Knox equation. Ion chromatography is a technique complimentary to the more commonly used reversed-phase and normal-phase HPLC and to atomic absorption and ion-coupled plasma (plasma spectrochemistry) techniques in pharmaceutical analysis.

APPARATUS

IC instruments closely resemble conventional HPLC instruments. Typical components include an 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, an optional suppressor or other forms of a post-column reaction system, a flow-through detector, and a data system ranging in complexity from an integrator to a computerized data system (*Figure 1*). Because mobile phases generally consist of dilute acids, alkalis, or salt solutions, the components in contact with the mobile phase and the sample are typically made from inert materials, such as polyetheretherketone (PEEK). Conventional HPLC systems also may be used provided that their components are compatible with the mobile phase and injected sample solutions. Following suitable preparation, the sample is introduced via the injection valve. After the optional chemical suppression or other post-column reaction on the column effluent, the analyte species are detected using conductivity, amperometry, UV/VIS, or other detection modes. Because IC uses a predominantly ionic mobile phase, a suppressor is often necessary prior to conductometric detection, although non-suppressed conductometric detection has been successfully used in pharmaceutical analysis.

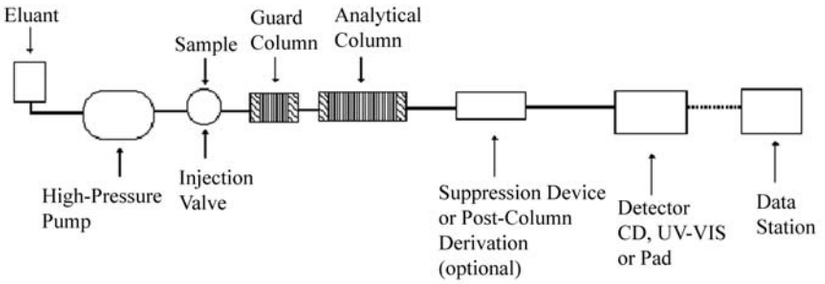

Fig. 1. Components of a typical IC system illustrated schematically; CD = conductivity detector and PAD = pulsed amperometric detector

Stationary and Mobile Phases

As IC has developed and matured as an instrumental technique, the number of ion-exchange materials developed for IC has increased, 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 predominately used as support materials for IC. Such materials have a higher stability with respect to extremes in pH and in many cases are compatible with organic solvents. Typically, separation of anions requires the use of polymer-based anion exchangers and dilute bases as mobile phases. However, for cation separations, the stability over the entire pH range that is typical of organic polymers is not necessary, because dilute acids serve as mobile phases. Therefore, silica-based cation exchangers that exhibit a significantly higher chromatographic efficiency are commonly used for the separation of cations.

Depending on the separation mode (ion exchange, ion exclusion, or ion-pair), different types of stationary phases are used. For ion exchange, the stationary phase is either an anion or a cation exchanger. Typically, a strong cation exchanger is used for the ion-exclusion separation of organic acids, and a reversed-phase stationary phase is used when ion-pair is the separation mode. The ion-exchange capacity of a resin is defined as the number of ion-exchange sites per weight equivalent of the column packing and is typically expressed in terms of mEq per g of resin. With ion exchange, the retention times for the analyte ions increase with increasing ion-exchange capacity of the resin. This effect can be partly compensated for by using mobile phases of higher ionic strength. Styrene/divinylbenzene copolymers, polymethacrylate, and polyvinyl resins are the substrate materials used in the manufacturing process of the polymer-based ion exchangers. Organic polymers are functionalized directly at their surface, with the exception of latex-based ion exchangers, where the totally porous latex particle acts as an ion-exchange material. Surface-functionalized, ‘‘pellicular’’ substrates show a much higher chromatographic efficiency compared with the fully functionalized resins.

With ion exchange, a mobile phase consisting of mono- or divalent ionic species, alone or mixed at an optimum ratio, is used to accomplish the separation. In ion-exclusion methods, particularly for organic acids, the mobile phase consists of mineral acids to maintain organic acids in their undisso-

ciated forms. Often, the nature of the analyte dictates the mobile phase and the detection mode used. Typical mobile phases used in IC are described below in the section on detectors.

Detectors

Conductivity detection is by far the most commonly employed mode of detection in IC. Although the original IC development work included the use of low-capacity ion-exchange resins for efficient chromatographic separation and conductometric detection of ions in a chemically suppressed mobile phase, the advances in column technologies as well as instrumentation development allow the use of high-capacity ion exchange today.

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, about 10 to 50 mM, used as the mobile phase in IC of anions is converted to H_2O (poor conductivity) when the column effluent containing NaOH flows through a suppressor device present in an acidic form. The analyte ionic species in the column effluent are converted from their sodium or other metal salt forms to highly conducting acid forms (due to higher equivalent conductance of hydrogen ions compared to other cations). Analogous reactions occur in the hydroxide form suppressor in IC of cations, wherein the acidic mobile phase is converted to water, and the analyte cations are converted to highly conducting hydroxide forms (due to higher equivalent conductance of hydroxide ions compared to other anions).

The reduced background conductance and the enhanced signal due to the ionic species result in an enhanced signal-to-noise ratio for the conductometric detection of ions in suppressed IC. This results in reduced background noise and increasing sensitivity and reproducibility of the analysis. The commonly used chemical suppression devices fall into three broad categories. In the first type, the reactions occur across an ion-exchange membrane with the regenerant ions furnished by either a chemical or as products of electrolysis of water. In the second type, the suppression reactions occur in a packed bed of high-exchange capacity resin material, with regeneration either by a chemical or by electrolysis of water. In the third type, although not commonly used, the suppression reactions occur as the eluant stream mixes with the flowing stream of high-capacity resin material.

For pharmaceutical analyses, suppressed conductometric detection may be used for detection of trace ions in high purity waters. The commonly used mobile phases for the separation of anions by suppressed IC include hydroxide ions or a mixture of bicarbonate and carbonate ions. The common mobile phases for separation of cations usually consist of mineral acids or methanesulfonic acid.

Ion-chromatographic analyses also can be performed without chemical suppression, in which case the analytical column effluent flows directly to a conductivity detector. The typical eluants 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 that of the eluant anion, and therefore, a positive peak is detected as the anions are carried through the detector. The equivalent conductance values of sodium, potassium, calcium, magnesium, and other common cations are significantly lower than that of the cation (H^+) in the eluant. In this instance, a negative peak is detected as the cations are carried through the detector.

Nonsuppressed IC is easier to perform, and it is a useful technique for determining ions of weak acids such as cyanide and sulfide, which are nonconductive after chemical suppression but show a higher baseline noise. Pharmaceutical analyses can be performed in the nonsuppressed mode because the quantification limits are usually in the upper mg per L to low percentage levels. While suppressor-based methodologies must often be implemented on the instrument systems specifically designed for this purpose, IC may be performed without the suppressor on an existing HPLC. This is possible because the commonly used eluants in IC include dilute bases or acids that are compatible for use on existing HPLC instruments. When this approach is considered, analysts are encouraged to consult the instrument manufacturer for applicability of the instrument for the IC analysis.

OTHER DETECTORS

Other commonly used detection modes in IC include pulsed amperometry, direct UV detection, or post-column derivatization followed by UV/VIS detection.

Pulsed Amperometric Detection Mode (PAD)—PAD uses a specialized mode of the conventional amperometric technique. This type of detector is commonly used for the detection of electroactive species, e.g., organic compounds such as carbohydrates, sugar alcohols, amino acids, and organic sulfur species. In PAD, analytes 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. Unlike conventional amperometry that suffers from electrode surface fouling, a rapidly repeating sequence of different working potentials, referred to as waveform, helps the removal of the products of redox reactions from the electrode surface. For details of application of IC using PAD in the analysis of mono- and oligosaccharides of glycoproteins, see *Glycoprotein Glycan Analysis* ⟨1084⟩.

Direct UV Detection—Direct UV Detection is used for inorganic and organic ions that possess a UV chromophore. These include organic acids, bromide, iodide, nitrate, nitrite, thiosulfate, and cyano-metal complexes. Analogous to the inverse conductometric detection of cations, UV detection may also be performed indirectly. This method is called indirect photometric chromatography (IPC).

Photometric Detection—Photometric detection involves derivatization of the column effluent with a color-forming reagent prior to detection with a visible wavelength. A classic example is the separation of metal ions in which the column effluent is derivatized with 4-(2-pyridylazo)-resorcinol followed by detection at 510 to 530 nm.

SAMPLE PREPARATION

Typically sample preparation for IC includes dilution or filtering through a 0.45-µm filter, or both. Under certain circumstances, samples may require removal of undesirable species through solid-phase extraction (SPE) techniques. For example, a highly alkaline sample can be neutralized by having it pass through a SPE cartridge packed with cation-exchange material in the acidic form.

PROCEDURE

Conductometric detection requires high purity water (generally, resistivity greater than 18 megohm-cm) and high-purity chemicals for the preparation of the mobile phase. For ion-pair separation with UV detection, water and mobile phase components of low UV absorbance should be used.

For ion exchange, the retention time of ions increases with a decrease in the ionic strength and valency (charge) of the mobile phase components. For example, at equimolar concentrations of sodium hydroxide or sodium carbonate mobile phase, capacity factors (k') for anions are smaller with sodium hydroxide as the mobile phase than with sodium carbonate as the mobile phase. Some mobile phases, such as sodium hydroxide, can absorb ambient carbon dioxide, resulting in its composition change and often in baseline artifacts. In this instance, care should be taken to prevent absorption of carbon dioxide by the sodium hydroxide mobile phase.

For ion exclusion, capacity factors of organic acids increase with an increase in ionic strength or concentration of mineral acids but decrease with the increase of the column temperature. Because permeation volume remains constant, these effects are usually small. Addition of a solvent such as acetonitrile shortens the retention of organic acids.

Like other HPLC techniques, IC systems are calibrated by plotting peak responses in comparison with known concentrations of a reference standard, using either an external or internal standardization procedure.▲*USP29*

BRIEFING

⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments, *USP 28* page 2682. On the basis of (1) comments received, (2) elimination of Federal Standard 209 E, and (3) advances in the field, it is proposed to revise and clarify this general information chapter. To reflect these changes, the title of the chapter has been changed to Microbiological Control and Monitoring Environments Used for the Manufacture of Healthcare Products. Many of the sections and tables of this information chapter have been revised: Table 5 and sections on *Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* and an *Overview of the Emerging Technologies for Advanced Aseptic Processing* have been eliminated; and new sections, *Physical Evaluation of Contamination Control Effectiveness* and *Sample Volumes for Active Air Monitoring,* have been added.

(AMB: R.S.Tirumalai) RTS—42245-1

Change to read:

⟨1116⟩~~MICROBIOLOGICAL EVALUATION OF CLEAN ROOMS AND OTHER CONTROLLED ENVIRONMENTS~~

▲MICROBIOLOGICAL CONTROL AND MONITORING ENVIRONMENTS USED FOR THE MANUFACTURE OF HEALTHCARE PRODUCTS▲*USP29*

Change to read:

~~The purpose of this informational chapter is to review the various issues that relate to aseptic processing of bulk drug substances, dosage forms, and in certain cases, medical devices; and to the establishment, maintenance, and control of the microbiological quality of controlled environments.~~

~~This chapter includes discussions on (1) the classification of a clean room based on particulate count limits; (2) microbiological evaluation programs for controlled environments; (3) training of personnel; (4) critical factors in design and implementation of a microbiological evaluation program; (5) development of a sampling plan; (6) establishment of microbiological Alert and Action levels; (7) methodologies and instrumentation used for microbiological sampling; (8) media and diluents used; (9) identification of microbial isolates; (10) operational evaluation via media fills; and (11) a glossary of terms. Excluded from this chapter is a discussion of controlled environments for use by licensed pharmacies in the preparation of sterile products for home use, which is covered under *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩.~~

~~There are alternative methods to assess and control the microbiological status of controlled environments for aseptic processing. Numerical values included in this chapter are not intended to represent absolute values or specifications, but are informational. Given the variety of microbiological sampling equipment and methods, one cannot reasonably suggest that the attainment of these values guarantees the needed level of microbial control or that excursions beyond values in this chapter indicate a loss of control. The improper application of microbiological sampling and analysis may cause significant variability and the potential for inadvertent contamination. Sampling media and devices, and methods indicated in this chapter, are not specifications but only informational.~~

~~A large proportion of sterile products are manufactured by aseptic processing. Because aseptic processing relies on the exclusion of microorganisms from the process stream and the prevention of microorganisms from entering open containers during filling, product bioburden as well as microbial bioburden of the manufacturing environment are important factors relating to the level of sterility assurance of these products.~~

In-Process Revision

▲The purpose of this informational chapter is to provide information and guidance relative to the monitoring and control of aseptic environments in which pharmaceutical dosage forms, aseptically produced active pharmaceutical ingredients, and, in certain cases, medical devices are manufactured. The guidance provided in this chapter and the monitoring parameters given for microbiological evaluation are to be applied to clean rooms and isolators used for aseptic processing and to other clean environments used for healthcare product manufacturing.

This chapter uses the total particulate air quality classifications provided by the International Standards Organization (ISO) in ISO 14644-1, -2, and -3. These ISO standards, like the United States Federal Standard 209E that they supercede, properly avoid providing guidance specific to the control and monitoring of environments for viable microorganisms. The international standards regarding the design and construction of clean rooms to meet certain total particulate air contamination requirements are broadly applicable to many industries including the electronics, defense, and healthcare industries. However, the healthcare product manufacturing industries, on the basis of many years of practical experience, have developed microbiological monitoring and control requirements unique to their particular requirements. Microbiologically controlled environments are used for a variety of purposes within the healthcare industry. Some uses of controlled environments, for example those used for aseptic processing, are far more critical than those used for other manufacturing operations (e.g., equipment and component preparation, limited bioburden control of nonsterile products, and processing for terminal sterilization). Therefore, requirements for aseptic processing environments for both manned clean rooms and isolators are treated separately from environments used for less critical applications. Excluded from this chapter is a discussion of controlled environments for use by licensed pharmacies in the preparation of sterile products for home use, which is covered in the two general test chapters, *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ and *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩.

There are a number of sampling methods that can be used to assess and control the microbiological status of controlled environments for aseptic processing. The numerical values for air, surface, and personnel monitoring included in this chapter are guidelines. Given the variety of microbiological sampling equipment and methods, one cannot reasonably suggest that the attainment of these values guarantees the needed level of microbial control or that excursions beyond values in this chapter indicate a loss of control. The assessment of risks associated with manufacturing environments must be made over a significant period of time, and excursions beyond the control levels recommended in this chapter may occasionally occur. The variables involved in microbiological monitoring, especially the lack of accuracy and precision, make it impossible to set firm limits applicable to product release or rejection. The improper application of microbiological sampling and analysis may cause significant variability and the potential for inadvertent contamination. Sampling media, devices, and methods indicated in this chapter are not compendial test methods and are provided for information only.

A large proportion of products labeled sterile products are manufactured by aseptic processing, rather than terminal sterilization. Because aseptic processing relies on the exclusion of microorganisms from the process stream and the prevention of microorganisms from entering open containers during filling, product bioburden as well as bioburden of the manufacturing environment are important factors gov-

erning the microbiological safety of these products. However, it is important to note that the terms aseptic and sterile are not synonymous. Sterile means the complete and unequivocal absence of viable microorganisms or organisms having the potential to reproduce. In the purest microbiological sense, aseptic means the prevention of infection accomplished by the exclusion of pathogenic organisms; however in the context of aseptic healthcare product manufacturing, the term aseptic describes the handling of sterilized materials in a controlled environment designed to maintain microbial contamination at levels known to present minimal risk.

It is not possible to create or maintain a manufacturing environment that is sterile in light of the present state-of-the-art. In any environment where human operators are present microbial contamination at some level is inevitable. Even the most cautious clean room environment design and operation will not obviate the shedding of microorganisms into the environment by human operators. Thus, an expectation of zero contamination at or during every aseptic processing operation is technically unrealistic. There is no way to prove that an aseptic processing environment or the product contact surfaces within that environment are sterile.

In recent years isolator technology has found a broad acceptance in healthcare manufacturing. Isolators are often considered a form of advanced aseptic manufacturing technology. Isolators more effectively control the potential of human-borne contamination, but most isolator designs cannot be proven to wholly exclude operator-shed contamination under all circumstances of use. Gloves, half-suits, or other manipulative devices used to conduct work within an isolator's enclosure may develop leaks resulting in contamination within the isolator enclosure. There is also the potential for introducing contamination into an isolator by operational mistake. It may not be possible to completely eliminate microbial contamination during isolator decontamination or gassing because isolators may contain complex or partially occluded surfaces. The isolator environment therefore cannot be considered a sterile environment, but rather an aseptic one.▲*USP29*

Change to read:

Establishment of Clean Room Classifications

~~The design and construction of clean rooms and controlled environments are covered in Federal Standard 209E. This standard of air cleanliness is defined by the absolute concentration of airborne particles. Methods used for the assignment of air classification of controlled environments and for monitoring of airborne particulates are included. This federal document only applies to airborne particulates within a controlled environment and is not intended to characterize the viable or nonviable nature of the particles.~~

~~The application of Federal Standard 209E to clean rooms and other controlled environments in the pharmaceutical industry has been used by manufacturers of clean rooms to provide a specification for building, commissioning, and maintaining these facilities. However, data available in the pharmaceutical industry provide no scientific agreement on a relationship between the number of nonviable particulates and the concentration of viable microorganisms.~~

~~The criticality of the number of nonviable particulates in the electronic industry makes the application of Federal Standard 209E a necessity, while the pharmaceutical industry has a greater concern for viable particulates (i.e., microorganisms) rather than total particulates as specified in Federal Standard 209E. A definite concern for counts of total particulates in injectable products exists in the pharmaceutical industry (see *Particulate Matter in Injections* ⟨~~788~~⟩).~~

~~The rationale that the fewer particulates present in a clean room, the less likely it is that airborne microorganisms will be present is accepted and can provide pharmaceutical manufacturers and builders of clean rooms and other controlled environments with engineering standards in establishing a properly functioning facility.~~

~~Federal Standard 209E, as applied in the pharmaceutical industry is based on limits of all particles with sizes equal to or larger than 0.5 µm. *Table 1* describes Airborne Particulate Cleanliness Classes in Federal Standard 209E as adapted to the pharmaceutical industry. The pharmaceutical industry deals with Class M3.5 and above. Class M1 and M2 relate to the electronic industry and are shown in *Table 1* for comparison purposes. It is generally accepted that if fewer particulates are present in an operational clean room or other controlled environment, the microbial count under operational conditions will be less, provided that there are no changes in airflow, temperature, and humidity. Clean rooms are maintained under a state of operational control on the basis of dynamic (operational) data.~~

▲The design and construction of clean rooms and controlled environments are covered in ISO 14644. This standard defines the performance of a clean environment with respect to the concentration of total particulates per unit vol-

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ume in that environment. ISO 14644 stipulates the total particulate counts required for a clean environment to meet the defined air quality classifications. The reader is referred to this standard regarding the design characteristics and certification of clean environments.

A concern for nonviable particulate contamination in injectable products exists in the pharmaceutical industry (see *Particulate Matter in Injections* ⟨788⟩. Unlike the situation with microbial contamination in which experimental data suggest that humans are the only significant source of microbial contamination in the classified clean room, nonviable particulates can also arise from processing equipment. Studies indicate that gowned humans slough off particulate and microbial contamination at a rather consistent ratio. However, the relationship between microbial (viable) and nonviable contamination does not hold for particulates shed by processing equipment. Where equipment is the primary source of particulate matter, the resulting particulates are essentially all nonviable.

The rationale that the fewer total particulates present in a clean room, the less likely it is that airborne microorganisms will be present is valid when human operators are the source of particulate matter. However, it is not possible to clearly distinguish between background total particulate contamination generated largely by mechanical operations and the total particulates contributed by personnel. Therefore, it is both commonplace and proper for clean room environmental monitoring programs to consist of a total particulate and a microbiological component.

Table 1 describes the clean room classifications commonly used in the pharmaceutical industry. The pharmaceutical industry utilizes clean rooms of ISO 14644 Classes 5–8.

Isolators present a different picture because personnel are excluded from the isolator, and manipulations are made utilizing glove-and-sleeve assemblies and half-suits made of thick, flexible plastic (such as polyvinyl chloride). Personnel have far less impact on the microbial quality of the environment within an isolator enclosure than they have on clean room environments.▲*USP29*

~~**Table 1. Airborne Particulate Cleanliness Classes**~~

~~Class Name~~	~~Particles equal to and larger than 0.5 µm~~		
~~SI~~	~~U.S. Customary~~	~~(m^3)~~	~~(ft^3)~~
~~M1~~	~~—~~	~~10.0~~	~~0.283~~
~~M1.5~~	~~1~~	~~35.3~~	~~1.00~~
~~M2~~	~~—~~	~~100~~	~~2.8~~
~~M2.5~~	~~10~~	~~353~~	~~10.0~~
~~M3~~	~~—~~	~~1,000~~	~~28.3~~
~~M3.5~~	~~100~~	~~3,530~~	~~100~~
~~M4~~	~~—~~	~~10,000~~	~~283~~
~~M4.5~~	~~1,000~~	~~35,300~~	~~1,000~~
~~M5~~	~~—~~	~~100,000~~	~~2,830~~
~~M5.5~~	~~10,000~~	~~353,000~~	~~10,000~~
~~M6~~	~~-~~	~~1,000,000~~	~~28,300~~
~~M6.5~~	~~100,000~~	~~3,530,000~~	~~100,000~~
~~M7~~	~~—~~	~~10,000,000~~	~~283,000~~

~~* Adapted from U.S. Federal Standard 209E, September 11, 1992 "Airborne Particulate Cleanliness Classes in Clean Rooms and Clean Zones."~~

▲**Table 1. Airborne Particulate Cleanliness Classes***

Class Name**	Particles ≥0.5 µm
ISO 14644	(m^3)
ISO Class 5	3,520
ISO Class 6	35,200
ISO Class 7	352,000
ISO Class 8	353,000,000

* Taken from ISO International Standard 14644 Part 1 published by the International Standards Organization, May 1999.
** The four ISO 14644-1 Classes given in Table 1 correspond very closely to former US Federal Standard 209E Classifications. The relationships are as follows: ISO 5-Class 100, ISO 6-Class 1000, ISO 7- Class 10,000, ISO 8- Class 100,000.

Specifications for air changes per hour and air velocities are not included in ISO 14644 nor were they in Federal Standard 209E. Typically, clean rooms of ISO Class 8/Class 100,000 are designed to provide a minimum of 20 air chang-

es per hour; clean rooms of ISO Class 7/Class 10,000 are designed to provide more than 50 air changes per hour; and clean rooms of ISO Class 5/Class 100 provide more than 100 air changes per hour, but some manufacturer's design criteria may differ. By diluting and removing contaminants, large volumes of air are likely to reduce airborne contamination in aseptic production. However, optimum conditions vary considerably depending on process characteristics. Typical air velocity standards given for Class 5 aseptic processing are 0.45 meters per second ±20%, measured approximately 30 cm from the filter face. These specifications should be used only as a guide in the design and operation of clean rooms because the precise correlation between air changes per hour, air velocity, and microbial control has not been satisfactorily established experimentally.

It is important to maintain a predominantly unidirectional (either vertical or horizontal) flow of air in a Class 5 clean room environment, particularly when products, product containers, and closures are exposed. When evaluating air movement within a clean room, studying airflow visually by so-called smoke studies or other suitable means is probably more useful than using absolute measures of airflow velocity and change rates. The so-called L-R method developed by Ljundqvist and Reinmuller provides a useful empirical method for evaluating and optimizing the prevention of airborne contamination and can serve as a basis for contamination risk evaluation and mitigation.

Air velocity and change rates are less important in isolators than in clean rooms because personnel in isolators—the major source of microbial contamination—are more carefully separated from the product, product containers, and closures. Air velocities substantially lower than those used in human-scale clean rooms have proven to be adequate in isolator systems. In zones within isolators where particulate matter poses a hazard to product quality, predominantly vertical or horizontal unidirectional airflow may be maintained. Experience, however, has shown that well-controlled mixing or turbulent airflow is satisfactory for many aseptic processes and for sterility testing within isolators (see *Sterility Testing—Validation of Isolator Systems* ⟨1208⟩).▲*USP29*

Change to read:

Importance of a Microbiological Evaluation Program for Controlled Environments

Monitoring of total particulate count in controlled environments, even with the use of electronic instrumentation on a continuous basis, does not provide information on the microbiological content of the environment. The basic limitation of particulate counters is that they measure particles of 0.5 µm or larger. While airborne microorganisms are not free-floating or single cells, they frequently associate with particles of 10 to 20 µm. Particulate counts as well as microbial counts within controlled environments vary with the sampling location and the activities being conducted during sampling. Monitoring the environment for nonviable particulates and microorganisms is an important control function because they both are important in achieving product compendial requirements for *Particulate Matter* and *Sterility* under *Injections* ⟨1⟩.

~~Microbial monitoring programs for controlled environments should assess the effectiveness of cleaning and sanitization practices by and of personnel that could have an impact on the bioburden of the controlled environment. Microbial monitoring, regardless of how sophisticated the system may be, will not and need not identify and quantitate all microbial contaminants present in these controlled environments. However, routine microbial monitoring should provide sufficient information to ascertain that the controlled environment is operating within an adequate state of control.~~

~~Environmental microbial monitoring and analysis of data by qualified personnel will permit the status of control to be maintained in clean rooms and other controlled environments. The environment should be sampled during normal operations to allow for the collection of meaningful data. Microbial sampling should occur when materials are in the area, processing activities are ongoing, and a full complement of operating personnel is on site.~~

~~Microbial monitoring of clean rooms and some other controlled environments, when appropriate, should include quantitation of the microbial content of room air, compressor air that enters the critical area, surfaces, equipment, sanitization containers, floors, walls, and personnel garments (e.g., gowns and gloves). The objective of the microbial monitoring program is to obtain representative estimates of bioburden of the environment. When data are compiled and analyzed, any trends should be evaluated by trained personnel. While it is important to review environmental results on the basis of recommended and specified frequency, it is also critical to review results over extended periods to determine whether trends are present. Trends can be visualized through the construction of statistical control charts that include alert and action levels. The microbial control of controlled environments can be assessed, in part, on the basis of these trend data. Periodic reports or summaries should be issued to alert the responsible manager.~~

~~When the specified microbial level of a controlled environment is exceeded, a documentation review and investigation should occur. There may be differences in the details of the investigation, depending on the type and processing of the product manufactured in the room. Investigation should include a review of area maintenance documentation; sanitization documentation; the inherent physical or operational parameters, such as changes in environ-~~

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~~mental temperature and relative humidity; and the training status of personnel involved. Following the investigation, actions taken may include reinforcement of training of personnel to emphasize the microbial control of the environment; additional sampling at increased frequency; additional sanitization; additional product testing; identification of the microbial contaminant and its possible source; and an evaluation of the need to reassess the current standard operating procedures and to revalidate them, if necessary.~~

~~Based on the review of the investigation and testing results, the significance of the microbial level being exceeded and the acceptability of the operations or products processed under that condition may be ascertained. Any investigation and the rationale for the course of action should be documented and included as part of the overall quality management system.~~

~~A controlled environment such as a clean zone or clean room is defined by certification according to a relevant clean room operational standard. Parameters that are evaluated include filter integrity, air velocity, air patterns, air changes, and pressure differentials. These parameters can affect the microbiological bioburden of the clean room operation. The design, construction, and operation of clean rooms varies greatly, making it difficult to generalize requirements for these parameters. An example of a method for conducting a particulate challenge test to the system by increasing the ambient particle concentration in the vicinity of critical work areas and equipment has been developed by Ljungquist and Reinmuller.[1] First, smoke generation allows the air movements to be visualized throughout a clean room or a controlled environment. The presence of vortices or turbulent zones can be visualized, and the airflow pattern may be fine tuned to eliminate or minimize undesirable effects. Then, particulate matter is generated close to the critical zone and *sterile field*. This evaluation is done under simulated production conditions, but with equipment and personnel in place.~~

~~Proper testing and optimization of the physical characteristics of the clean room or controlled environment is essential prior to completion of the validation of the microbiological monitoring program. Assurance that the controlled environment is operating adequately and according to its engineering specifications will give a higher assurance that the bioburden of the environment will be appropriate for aseptic processing. These tests should be repeated during routine certification of the clean room or controlled environment and whenever changes made to the operation, such as personnel flow, processing, operation, material flow, air handling systems, or equipment layout, are determined to be significant.~~

▲Total particulate monitoring may provide a better means of evaluating the overall quality of the environment in isolators than in conventional clean rooms. The superior exclusion of human-borne contamination provided by isolators results in a ratio between viable and nonviable contamination that is biased heavily in the direction of nonviable particulates in the isolator environment. Total particulate counting in an isolator is likely to provide an immediate indicator of changes in contamination level within the enclosed environment. Microbial monitoring programs for aseptic processing environments should assess the effectiveness of cleaning and sanitization practices of personnel that could have an impact on the bioburden of the controlled environment. Because isolators are typically decontaminated using an automatic vapor or gas generation system, microbial monitoring is much less important in establishing their efficiency in eliminating bioburden. These automatic decontamination systems are validated directly using an appropriate biological indicator challenge and are controlled to defined exposure parameters during routine use to ensure consistent decontamination performance.

Microbial monitoring will not and need not identify and quantify all microbial contaminants present in these controlled environments. Microbiological monitoring of a clean room is technically a semiquantitative exercise because a truly quantitative evaluation of the environment is not possible given the limitations in sampling equipment, lack of precision of the enumeration methods, and the restricted sample volumes that can be effectively analyzed. Routine microbial monitoring, however, should provide sufficient information to ascertain that the aseptic processing environment is operating within an adequate state of control. The real value of a microbiological monitoring program lies in the consistent, qualitative assessment of environmental conditions over time. Monitoring programs can detect changes in the contamination incidence rate; such changes may be indicative of changes in the state-of-control within the environment.

Environmental microbial monitoring and analysis of data by qualified personnel will assist in ensuring that a suitable state-of-control is maintained in aseptic processing environments. The environment should be sampled during normal operations to allow for the collection of meaningful, process-related data. Microbial sampling should occur when materials are in the area, processing activities are ongoing, and a full complement of operating personnel are within the aseptic processing environment.

~~[1] Interaction Between Air Movements and the Dispersion of Contaminants: Clean Zones with Unidirectional Air Flow, Journal of Parenteral Science and Technology, 47(2), 1993.~~

Microbial monitoring of clean rooms and isolators should include monitoring of compressed gases, surfaces, room/enclosure air, and any other materials and equipment that might produce a risk of contamination. The analysis of contamination trends within an aseptic environment has long been a component of the environmental control program of healthcare product manufacturing environments. In aseptic processing environments, and particularly in ISO Class 5 environments, contamination is infrequently observed; and in isolator enclosures, because of their superior exclusion of human borne contamination, contamination is rarer still. However, given the criticality of these environments, even minor changes in their contamination-control-incident rates can be significant. Therefore, frequent careful review of monitoring data is essential. In less critical environments where microbial contamination may be higher, changes in incident rates should nonetheless be noted, investigated, and corrected.

When contamination incident rates increase from an established norm, documentation review and investigation should occur. Although there may be differences in the details of the investigation, depending on the type and processing of the product manufactured in the clean room or isolator, investigation should include a review of the following: area maintenance documentation; sanitization/decontamination documentation; the occurrence of nonroutine events, the inherent physical or operational parameters, such as changes in environmental temperature and relative humidity; and the training status of personnel involved.

In isolator systems, the loss of glove integrity or the accidental introduction of material that has not been decontaminated are among the most probable causes of detectable microbial contamination. Following the investigation, defined actions should be taken to correct or eliminate the most probable causes of contamination. In aseptic processing applications, given the relative rarity of contamination events in modern facilities, the investigation will often prove inconclusive. When corrective actions are undertaken, they may include reinforcement of training of personnel to emphasize acceptable gowning and aseptic techniques and the microbial control of the environment. Some additional microbiological sampling at an increased frequency may be implemented, but this may not be appropriate in aseptic processing because intrusive or overly intensive sampling may entail a contamination risk in and of itself. Other measures that may be considered to better control microbial contamination include additional sanitization, use of different sanitizing agents, and identification of the microbial contaminant and its possible source. The investigation and the rationale for the course of action chosen as a result of the investigation must be carefully and comprehensively documented.▲*USP29*

Add the following:

▲Physical Evaluation of Contamination Control Effectiveness

As previously stated, clean environments should be certified as described in ISO 14644 to meet their defined classification requirements. The design, construction, and operation of clean rooms vary greatly, making it difficult to generalize requirements for parameters such as filter integrity, air velocity, air patterns, air changes, and pressure differential. However, in particularly critical applications, such as aseptic processing, a more structured approach to physical risk assessment may be appropriate.

A method for assessing the ability of a clean room to resist the effects of contamination emanating from personnel and the environment has been developed by Ljundqvist and Reinmuller [see Interaction Between Air Movements and the Dispersion of Contaminants: Clean Zones with Unidirec-

tional Air Flow, *Journal of Parenteral Science and Technology,* **1993,** *47*(2)]. This method, known as the L-R method, challenges the air filtration and ventilation system by increasing particle concentration in the vicinity of critical work areas and equipment. First, smoke generation allows the air movements to be visualized throughout a clean room or a controlled environment. The presence of vortices or turbulent zones can be visualized, and the airflow pattern may be fine-tuned to minimize undesirable effects. Following visual optimization of airflow, particulate matter is generated close to the critical zone and sterile field. This evaluation is done under simulated production conditions, but with equipment and personnel in place. This type of test can also be used to evaluate the ability of isolator systems, particularly so-called open isolator systems, to resist the effects of contamination generated in the area surrounding the isolator system. It is important to note that the visual evaluation of air movement within clean rooms is a subjective process. Elimination of turbulence or vortices is generally not possible in operational clean rooms containing personnel and equipment. In all cases hard data in the form of total particulate and microbiological monitoring as well as medial fill results take precedence over visualization of airflow patterns using smoke or other suitable techniques.

Proper testing and optimization of the physical characteristics of the clean room or isolator are essential prior to the implementation of the microbiological monitoring program. Assurance that the clean room or isolator is operating in compliance with its predetermined engineering specifications will provide confidence that the ability of the system to control the bioburden and nonviable particulate matter will be appropriate for it's intended use. These tests should be repeated during routine certification of the clean room or isolator and whenever changes made to the operation, such as personnel flow, equipment operation, material flow, air-handling systems, or equipment layout, are determined to be significant.▲*USP29*

Change to read:

Training of Personnel

~~Aseptically processed products require manufacturers to pay close attention to detail and to maintain rigorous discipline and strict supervision of personnel in order to maintain the level of environmental quality appropriate for the sterility assurance of the final product.~~

~~Training of all personnel working in controlled environments is critical. This training is equally important for personnel responsible for the microbial monitoring program, where contamination of the clean working area could inadvertently occur during microbial sampling. In highly automated operations, the monitoring personnel may be the employees who have the most direct contact with the critical zones within the processing area. Monitoring of personnel should be conducted before or after working in the processing area.~~

~~Microbiological sampling has the potential to contribute to microbial contamination due to inappropriate sampling techniques. A formal personnel training program is required to minimize this risk. This formal training should be documented for all personnel entering controlled environments.~~

~~Management of the facility must assure that all personnel involved in operations in clean rooms and controlled environments are well versed in relevant microbiological principles. The training should include instruction on the basic principles of aseptic processing and the relationship of manufacturing and handling procedures to potential sources of product contamination. This training should include instruction on the basic principles of microbiology, microbial physiology, disinfection and sanitation, media selection and preparation, taxonomy, and sterilization as required by the nature of personnel involvement in aseptic processing. Personnel involved in microbial identification will require specialized training on required laboratory methods. Additional training on the management of the environmental data collected must be provided to personnel. Knowledge and understanding of applicable standard operating procedures is critical, especially those standard operating procedures relating to corrective measures that are taken when environmental conditions so dictate. Understanding of regulatory compliance policies and each individual's responsibilities with respect to good manufacturing practices (GMPs) should be an integral part of the training program as well as training in conducting investigations and in analyzing data.~~

~~The major source of microbial contamination of controlled environments is the personnel. Contamination can occur from the spreading of microorganisms by individuals, particularly those with active infections. Only healthy individuals should be permitted access to controlled environments.~~

~~These facts underscore the importance of good personal hygiene and a careful attention to detail in the aseptic gowning procedure used by personnel entering the controlled environment. Once these employees are properly gowned—including complete facial coverage—they must be careful to maintain the integrity of their gloves and suits at all times. Since the major threat of contamination of product being aseptically processed comes from the operating personnel, the control of microbial contamination associated with these personnel is one of the most important elements of the environmental control program.~~

~~The importance of thorough training of personnel working in controlled environments, including aseptic techniques, cannot be overemphasized. The environmental monitoring program, by itself, will not be able to detect all events in aseptic processing that~~

~~could compromise the microbiological quality of the environment. Therefore, periodic media-fill or process-simulation studies to revalidate the process are necessary to assure that the appropriate operating controls and training are effectively maintained.~~

▲Given the central role that good personnel performance plays in the control of contamination in clean environments, proper training and supervision play a crucial part in contamination control. Aseptic processing is the most critical activity conducted in microbiological controlled environments, and manufacturers must pay close attention to the details in all aspects of this endeavor. The maintenance of rigorous discipline and strict supervision of personnel is essential in order to ensure a level of environmental quality appropriate for aseptic processing.

Training of all personnel working in controlled environments is critical. This training is equally important for personnel responsible for the microbial monitoring program, where contamination of the clean working area could inadvertently occur during microbial sampling. In highly automated operations, the monitoring personnel may be the employees who have the most direct contact with the critical zones within the processing area. Microbiological sampling has the potential of contributing to microbial contamination due to inappropriate sampling techniques or placement of personnel in or near the critical zone more frequently than required by the production activity itself. A formal personnel training program is required to minimize this risk. This formal training should be documented for all personnel entering controlled environments.

Management of the facility must assure that all personnel involved in operations in clean rooms and isolators are well versed in relevant microbiological principles. The training should include instruction on the basic principles of aseptic technique and should emphasize the relationship of manufacturing and handling procedures to potential sources of product contamination. Those individuals supervising, auditing, or inspecting microbiological control and monitoring activities should be knowledgeable regarding the basic principles of microbiology, microbial physiology, disinfection and sanitation, media selection and preparation, taxonomy, and sterilization. Ideally both supervisors and inspectors should have academic training in medical or environmental microbiology. Sampling personnel, as well as those individuals working in clean rooms, should be knowledgeable regarding their responsibilities in minimizing the release of microbial contamination into the environment. Personnel involved in microbial identification will require specialized training on required laboratory methods. Additional training should be provided concerning the management of the collection of environmental data. Knowledge and understanding of applicable standard operating procedures is critical, especially those standard operating procedures relating to corrective measures that are taken when environmental conditions so dictate. Understanding of contamination control principles and each individual's responsibilities with respect to good manufacturing practices (GMP), as well as training in conducting investigations and in analyzing data, should be an integral part of the training program.

The major source of microbial contamination of controlled environments is the personnel. Contamination can occur from the spreading of microorganisms by individuals, particularly those with active infections. Only healthy individuals should be permitted access to controlled environments.

The importance of good personal hygiene and a careful attention to detail in the aseptic gowning procedure used by personnel entering the controlled environment cannot be overemphasized. Gowning requirements will differ depending upon the use of the controlled environment being entered. Aseptic processing environments are the most critical and require the use of sterilized gowns with the best available filtration properties. The fullest possible facial

coverage is desirable for aseptic processing environments, and sleeve covers or tape should be considered to minimize leaks at the critical glove/sleeve junction. Once employees are properly gowned they must be careful to maintain the integrity of their gloves and suits at all times. Since the major threat of contamination of product comes from the operating personnel, the control of microbial contamination associated with these personnel is one of the most important elements of the environmental control program. Operators working with isolator systems for aseptic processing are not required to wear sterile, clean room gowns. However, aseptic technique and employee-borne contamination are the principal hazards to safe aseptic operations in isolators as well as in conventional clean rooms. Glove-and-sleeve assemblies can develop leaks that might allow the mechanical transfer of microorganisms to the product. A second glove, worn either under or over the primary isolator glove, could provide an additional level of safety against glove leaks or could act as a hygiene measure. In addition, operators must understand that aseptic technique is an absolute requirement for all manipulations performed with gloves within isolator systems.

The importance of thorough training and careful supervision of personnel working in controlled environments, including use of aseptic techniques, cannot be overemphasized. The environmental monitoring program, by itself, will not be able to detect all events in aseptic processing that could compromise the microbiological quality of the environment. Therefore, periodic media-fill or process simulation studies to revalidate the process are necessary, as is thorough, ongoing supervision of operations, to ensure that the appropriate operating controls and training are effectively maintained.▲*USP29*

Change to read:

Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program

~~An environmental control program should be capable of detecting an adverse drift in microbiological conditions in a timely manner that would allow for meaningful and effective corrective actions. It is the responsibility of the manufacturer to develop, initiate, implement, and document such a microbial environmental monitoring program.~~

~~Although general recommendations for an environmental control program will be discussed, it is imperative that such a program be tailored to specific facilities and conditions. A general microbiological growth medium such as Soybean Casein Digest Medium should be suitable in most cases. This medium may be supplemented with additives to overcome or to minimize the effects of sanitizing agents, or of antibiotics if used or processed in these environments. The detection and quantitation of yeasts and molds should be considered. General mycological media, such as Sabouraud's, Modified Sabouraud's, or Inhibitory Mold Agar are acceptable. Other media that have been validated for promoting the growth of fungi, such as Soybean Casein Digest Agar, can be used. In general, testing for obligatory anaerobes is not performed routinely. However, should conditions or investigations warrant, such as the identification of these organisms in sterility testing facilities, more frequent testing is indicated. The ability of the selected media to detect and quantitate these anaerobes or microaerophilic microorganisms should be evaluated.~~

~~The selection of time and incubation temperatures is made once the appropriate media have been selected. Typically, incubation temperatures in the 22.5 ± 2.5° and 32.5 ± 2.5° ranges have been used with an incubation time of 72 and 48 hours, respectively. Sterilization processes used to prepare growth media for the environmental program should be validated and, in addition, media should be examined for sterility and for growth promotion as indicated under *Sterility Tests* ⟨71⟩. In addition, for the *Growth Promotion* test, representative microflora isolated from the controlled environment or ATCC strain preparations of these isolates may also be used to test media. Media must be able to support growth when inoculated with less than 100 colony-forming units (cfu) of the challenge organisms.~~

~~An appropriate environmental control program should include identification and evaluation of sampling sites and validation of methods for microbiological sampling of the environment.~~

~~The methods used for identification of isolates should be verified using indicator microorganisms (see *Microbial Limits* ⟨61⟩).~~

▲Since the advent of comprehensive environmental monitoring programs in the healthcare product manufacturing industry, the need for these programs to capture adverse trends or drifts has been emphasized. In a modern aseptic processing environment—either isolators or conventional clean rooms—contamination has become increasingly rare. Nevertheless, a monitoring program must be able to detect contamination risk and to apply appropriate countermeasures. Although general recommendations for an environ-

mental monitoring program will be discussed, it is imperative that such a program be tailored to specific facilities and conditions.

Selection of Growth Media—In most cases, a general microbiological growth medium that supports the growth of a wide range of bacteria, yeasts, and molds, such as Soybean–Casein Digest Medium (SCDM), should be suitable for environmental monitoring. This medium may be supplemented with additives to overcome or to minimize the effects of sanitizing agents or of antibiotics if used or processed in these environments. The specific detection of yeasts and molds should be considered; however, the SCDM medium will usually not be overgrown by bacteria. If necessary, general mycological media, such as Sabouraud's, Modified Sabouraud's, or Inhibitory Mold Agar are acceptable. In general, monitoring for strict anaerobes is not performed as they would be a minor component of other microbial populations. However, should conditions or investigations warrant, i.e., conditions such as the identification of these organisms in sterility testing facilities or in sterility test results, then testing for anaerobes would be indicated. The ability of any media used in environmental monitoring, including those selected for their ability to recover specific types of organisms, must be evaluated for their ability to support growth as indicated under *Sterility Tests* ⟨71⟩.

Selection of Culture Conditions—The selection of time and incubation temperatures is made once the appropriate media have been selected. Typically for general microbiological growth media such as SCDM, incubation temperatures in the 22.5 ± 2.5° and 32.5 ± 2.5° ranges have been used with an incubation time not less than 72 hours. There is no data suggesting precise optimum incubation temperatures. Mesophilic bacteria and mold common to the typical facility environment are generally capable of growing over a rather wide range of temperatures. Sterilization processes used to prepare growth media for the environmental program should be validated. When special or selective media are used for monitoring incubation conditions, they should reflect published technical requirements. Contamination should not be introduced into a manufacturing clean room as a result of using contaminated sampling media or equipment. Of particular concern is the use of aseptically prepared sampling media. Wherever possible, sampling media and its wrapping should be terminally sterilized by moist heat, radiation, or other suitable means. If aseptically prepared media must be used, pre-incubation and 100% visual inspection of all sampling media prior to introduction into the clean room are required.▲*USP29*

Change to read:

Establishment of Sampling Plan and Sites

~~During initial start-up or commissioning of a clean room or other controlled environment, specific locations for air and surface sampling should be determined. Consideration should be given to the proximity to the product and whether air and surfaces might be in contact with a product or sensitive surfaces of container-closure systems. Such areas should be considered critical areas requiring more monitoring than non-product-contact areas. In a parenteral vial-filling operation, areas of operation would typically include the container-closure supply, paths of opened containers, and other inanimate objects (e.g., fomites) that personnel routinely handle.~~

~~The frequency of sampling will depend on the criticality of specified sites and the subsequent treatment received by the product after it has been aseptically processed. *Table 2* shows suggested frequencies of sampling in decreasing order of frequency of sampling and in relation to the criticality of the area of the controlled environment being sampled.~~

~~Table 2. Suggested Frequency of Sampling on the Basis of Criticality of Controlled Environment~~

~~Sampling Area~~	~~Frequency of Sampling~~
~~Class 100 or better room designations~~	~~Each operating shift~~
~~Supporting areas immediately adjacent to Class 100 (e.g., Class 10,000)~~	~~Each operating shift~~
~~Other support areas (Class 100,000)~~	~~Twice/week~~
~~Potential product/container contact areas~~	~~Twice/week~~
~~Other support areas to aseptic processing areas but non product contact (Class 100,000 or lower)~~	~~Once/week~~

~~As manual interventions during operation increase, and as the potential for personnel contact with the product increases, the relative importance of an environmental monitoring program increases. Environmental monitoring is more critical for products that are~~

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~~aseptically processed than for products that are processed and then terminally sterilized. The determination and quantitation of microorganisms resistant to the subsequent sterilization treatment is more critical than the microbiological environmental monitoring of the surrounding manufacturing environments. If the terminal sterilization cycle is not based on the overkill cycle concept but on the bioburden prior to sterilization, the value of the bioburden program is critical.~~

~~The sampling plans should be dynamic with monitoring frequencies and sample plan locations adjusted based on trending performance. It is appropriate to increase or decrease sampling based on this performance.~~

▲During initial start-up or commissioning of a clean room or other controlled environment, specific locations for air and surface sampling should be determined: consideration should be given to the proximity to the product and whether air and surfaces might be in contact with a product or sensitive surfaces of container–closure systems. In aseptic processing the area in which containers, closures, and product are exposed to the environment is often called the critical zone. The entire critical zone should be treated as a sterile field with regard to aseptic operations. A nonsterile object, including the operator's gloved hands or isolator glove, should never be brought into contact with a sterile product, container closure, filling station, or conveying equipment before or during aseptic processing operations. Operators and environmental monitoring personnel should never touch sterile parts, conveyors, filling needles, part hoppers, or any other equipment that is in the product-delivery pathway.

The frequency of sampling depends upon the manufacturing process conducted within an environment. Classified environments used only to provide a lower overall level of bioburden in nonsterile product manufacturing areas require relatively infrequent environmental monitoring. Classified environments in which closed manufacturing operations are conducted, including fermentation and many chemical processes, require fewer monitoring sites and less frequent monitoring because the risk to these processes from microbial contamination originating from the surrounding environment is comparatively low. Microbiological monitoring of environments in which products are filled prior to terminal sterilization is generally less critical than the monitoring of aseptic processing areas. The amount of monitoring required in preterminal sterilization filling operations depends upon the susceptibility of the product being filled to survival and proliferation of microbial contamination. The identification and estimated number of microorganisms resistant to the subsequent sterilization treatment may be more critical than the microbiological monitoring of the surrounding manufacturing environments. It is not possible to recommend microbial control levels for each type of manufacturing environment. The levels established for one ISO Class 7 area, for example, may be inappropriate for another ISO Class 7 environment depending upon the production activities undertaken in each. The user should conduct a risk analysis and develop a rationale for the sampling locations and frequencies selected for each controlled environment. The classification of a clean room is important in establishing control levels. However, this does not imply that all rooms of the same classification should have the same control levels and the same frequency of monitoring, as the monitoring should reflect the microbiological control requirements of manufacturing or processing activities conducted in the area. Formal risk assessment techniques can result in a more scientifically valid contamination control program.

Table 2 suggests frequencies of sampling in decreasing order of frequency of sampling and in relation to the criticality or product risk of the area of the controlled environment being sampled.

Environmental monitoring sampling plans should be dynamic with monitoring frequencies and sample-plan-location-adjustments based on the observed incidence of contamination and ongoing risk analysis. On the basis of long-term observations, it may be appropriate to increase

or decrease sampling at a given location or to eliminate a sampling location altogether. Oversampling of an environment can be as deleterious to the control of contamination as undersampling. Careful consideration of risk and reduction of contamination sources can assist in right-sizing the sampling intensity.

Table 2. Suggested Frequency of Sampling for Aseptic Processing Areas

Sampling Area	Frequency of Sampling
ISO Class 5 or better room designations	Each operating shift (if a Class 5 designation rated hood is used for control of nonviable particulates, microbiological testing is not required)
Isolator systems: active air sampling	Once per manufacturing day or product lot
Isolator systems: surface monitoring	At the end of each monitoring campaign
Aseptic processing area adjacent to ISO Class 5 (e.g., ISO Class 7)	Each operating shift
Other support areas in aseptic processing (ISO Class 8)	Twice/week
Other less critical support areas in aseptic processing (ISO Class 8)	Once/week
Nonaseptic closed operations (ISO Class 7)	Twice/month
Nonaseptic open operations with moderate microbial risk (ISO Class 7)	Once/week
Nonaseptic open operations with higher microbial risk (ISO Class 7)	Once/lot
Nonaseptic closed operations (ISO Class 8)	Once/quarter
Nonaseptic open operations with low microbial risk	Once/quarter
Nonaseptic open operations with moderate microbial risk	Once/month

▲*USP29*

Change to read:

~~Establishment of Microbiological Alert and Action Levels in Controlled Environments~~

▲Selection of Sample Sites within Clean Rooms and Aseptic Processing Areas▲*USP29*

~~The principles and concepts of statistical process control are useful in establishing Alert and Action levels and in reacting to trends.~~

~~An *Alert level* in microbiological environmental monitoring is that level of microorganisms that shows a potential drift from normal operating conditions. Exceeding the Alert level is not necessarily grounds for definitive corrective action, but it should at least prompt a documented follow-up investigation that could include sampling plan modifications.~~

~~An *Action level* in microbiological environmental monitoring is that level of microorganisms that when exceeded requires immediate follow-up and, if necessary, corrective action.~~

~~*Alert levels* are usually based upon historical information gained from the routine operation of the process in a specific controlled environment.~~

~~In a new facility, these levels are generally based on prior experience from similar facilities and processes; and at least several weeks of data on microbial environmental levels should be evaluated to establish a baseline.~~

~~These levels are usually re-examined for appropriateness at an established frequency. When the historical data demonstrate improved conditions, these levels can be re-examined and changed to reflect the conditions. Trends that show a deterioration of the environmental quality require attention in determining the assignable cause and in instituting a corrective action plan to bring the conditions back to the expected ranges. However, an investigation should be implemented and an evaluation of the potential impact this has on a product should be made.~~

▲ISO 14644 suggests a grid approach for the classification of clean rooms. This approach is appropriate to certify the performance of a classified environment against its design objective. A grid approach, however, is generally less valuable for the evaluation of microbial contamination within clean rooms. Microbial contamination is strongly associated

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with personnel, therefore microbiological monitoring of unmanned environments is generally of little value because it is not representative of microbiological contamination control during actual production operations.

Microbiological sampling sites are best selected when human activity during manufacturing operations are considered. Careful observation and mapping of a clean room during the qualification phase can provide information concerning the movement and positioning of personnel within these rooms. Such observation can also yield important information about the most frequently conducted manipulations and interventions.

Other areas of concern relative to introduction of contamination into clean rooms are at entry points where equipment and materials move from areas of lower classification to those of higher classification. Therefore, areas within and around doors and airlocks should be included in the monitoring scheme. It has been customary to sample walls and floors, and indeed sampling at these locations provide information relative to the effectiveness of the sanitization program. Sampling at these locations, however, may be relatively infrequent because contamination at these locations is unlikely to affect product. Operators should never touch floors and walls during operation; this would eliminate mechanical transmission of contamination from these surfaces to product. Furthermore, because the most likely route of contamination of product is via an airborne route, the samples most critical to risk assessment are those that measure airborne contamination.

Monitoring of surfaces within the critical zone is also typically done, although this should be done only at the end of operations. Residues of media or diluent from wet swabs on surfaces should be avoided as this could lead to microbial proliferation. Removing any excess diluent or media requires personnel intervention and movement, which can result in release of microbial contamination into the critical zone and disrupt airflow.▲*USP29*

Change to read:

~~**Microbial Considerations and Action Levels for Controlled Environments**~~

▲Establishment of Microbiological Control Parameters in Clean Rooms and Isolators Used for Aseptic Processing▲*USP29*

~~Classification of clean rooms and other controlled environments is based on Federal Standard 209E based on total particulate counts for these environments. The pharmaceutical and medical devices industries have generally adopted the classification of Class 100, Class 10,000, and Class 100,000, especially in terms of construction specifications for the facilities.~~

~~Although there is no direct relationship established between the 209E controlled environment classes and microbiological levels, the pharmaceutical industry has been using microbial levels corresponding to these classes for a number of years; and these levels have been those used for evaluation of current GMP compliance.[2] These levels have been shown to be readily achievable with the current technology for controlled environments. There have been reports and concerns about differences in these values obtained using different sampling systems, media variability, and incubation temperatures. It should be recognized that, although no system is absolute, it can help in detecting changes, and thus trends, in environmental quality. The values shown in *Tables 3*, *4*, and *5* represent individual test results and are suggested only as guides. Each manufacturer's data must be evaluated as part of an overall monitoring program.~~

~~**Table 3. Air Cleanliness Guidelines in Colony-Forming Units (cfu) in Controlled Environments (Using a Slit-to-Agar Sampler or Equivalent)**~~

~~Class*~~		~~cfu per cubic meter of air**~~	~~cfu per cubic feet of air~~
~~SI~~	~~U.S. Customary~~		
~~M3.5~~	~~100~~	~~Less than 3~~	~~Less than 0.1~~
~~M5.5~~	~~10,000~~	~~Less than 20~~	~~Less than 0.5~~
~~M6.5~~	~~100,000~~	~~Less than 100~~	~~Less than 2.5~~

~~* As defined in Federal Standard 209E, September 1992.~~
~~** A sufficient volume of air should be sampled to detect excursions above the limits specified.~~

~~[2] NASA, 1967—Microbiology of Clean Rooms.~~

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~~**Table 4. Surface Cleanliness Guidelines of Equipment and Facilities in cfu in Controlled Environments**~~

~~Class~~		~~cfu per Contact Plate*~~
~~SI~~	~~U.S. Customary~~	
~~M3.5~~	~~100~~	~~3 (including floor)~~
~~M5.5~~	~~10,000~~	~~5~~
		~~10 (floor)~~

~~* Contact plate areas vary from 24 to 30 cm^2. When swabbing is used in sampling, the area covered should be greater than or equal to 24 cm^2 but no larger than 30 cm^2.~~

~~**Table 5. Surface Cleanliness Guidelines in Controlled Environments of Operating Personnel Gear in cfu**~~

~~Class~~		~~cfu per Contact Plate*~~	
~~SI~~	~~U.S. Customary~~	~~Gloves~~	~~Personnel Clothing & Garb~~
~~M3.5~~	~~100~~	~~3~~	~~5~~
~~M5.5~~	~~10,000~~	~~10~~	~~20~~

~~* See in *Table 4* under (*).~~

▲*Table 3* below, shows the microbial levels suggested in the EU GMPs for classified environments. These values can serve as a useful starting point in establishing control parameters. It is important to consider that the values for Class A and Class B environments, which are given as 1 and 3 cfu, respectively, are considered average values from many samples taken over an extended period of time. It should be noted that the European classification scheme is somewhat different from ISO 14644. European Class A can be considered equivalent to ISO Class 5. European Class B, however, has no real analogue within the ISO 14644 classification scheme because it is defined as Class 100 at rest and Class 10,000 in operation. The Class B environment is generally used for the area surrounding the aseptic processing critical zone (ISO 5/EU A) and therefore is most similar to ISO Class 7 or traditional Class 10,000.

It has been customary since the early 1980s to establish alert and action levels for environmental monitoring. However, in recent years the numerical spread between alert and action levels has become quite small. It is generally accepted that growth and recovery microbiological assays have normal variability in the range of ± 0.5 $\log_{10}$. Studies on active microbiological air samplers indicate that variability of as much as 10-fold is possible among commonly used sampling devices. As a result of this inherent variability and indeterminate error, differences between, for example, an alert level of 1 cfu and an action level of 3 cfu are not analytically significant. Therefore, caution is in order in ascribing differences to microbial sampling results that are within expected variability of measurement. In a practical sense, numerical values that vary by as much as 5- to 10-fold may not be significantly different.

Because of the limited accuracy and precision of microbial growth and recovery assays, in evaluating microbiological risk it is more logical to consider contamination incidence rate than absolute numbers of cfu detected in any single sample. Mean incidence rates should be determined for each clean room environment, and changes in incidence rate at any given site or within a given room may indicate the need for corrective action. Within the Class 5 critical zone, airborne and surface contamination incidence rates of 1% or less should be readily attainable. Incidence rates for isolator systems should be significantly lower and can be expected to be $< 0.1\%$.

Contamination observed at multiple sites within an environment within a single sampling period may be indicative of increased contamination risk to product and should be carefully evaluated. The appearance of contamination at multiple sites may also arise from poor sampling technique. Therefore, careful review of the situation is in order before conclusions are drawn regarding potential loss of control. It is important to consider that resampling of an environment several days after contamination is recovered at multiple locations is of little value because the conditions present on one sampling occasion may not be accurately duplicated on another.

Table 3. EU Recommended Microbiological Monitoring Levels for Aseptic Processing*

Room Grade	Active Air Sample	Settling Plate (9 cm) 4-hr Exposure	Contact Plate	Glove Sample
A (ISO Class 5)	<1	<1	<1	<1
B	10	5	5	5
C (ISO Class 7)	100	50	25	—
D (ISO Class 8)	200	100	50	—

* The values listed for Grade A environments are average values over a significant period of time. Colonies appear only as whole integers.
The values given for Class B, C, and D environments are for general reference only. Users should base their expectations on actual observed results.
Surface samples may also be taken on clean room garments. In this case the average should be <1 for these sample sites as well.

Table 4. Recommended Contamination Incident Rates for Aseptic Processing*

Grade	Active Air Sample	Settle Plate (9 cm) 4-hr exposure	Contact Plate or Swab	Glove or Garment
Isolator (ISO Class 5 or better)	<0.1%	<0.1%	<0.1%	<0.1%
A/ISO Class 5	<1%	<1%	<1%	<1%
B	<3%	<3%	<3%	<3%
C/ISO Class 7	<5%	<5%	<5%	<5%
D/ISO Class 8	<10%	<10%	<10%	<10%

* The incidence rates apply only to aseptic processing environments. Clean rooms that are used for other applications such as control of bioburden in closed processing areas, rooms surrounding isolators or fermentors, isolators used primarly for containment, manufacture of most terminally sterilized products, or solid dosage form manufacturing areas can have more liberal contamination incidence rates. In these applications where asepsis is not claimed and bioburden control is the objective, incidence rates can and should be established on a case-by-case basis supported by risk analysis.

Given the inherent variability associated with microbial sampling methods, incidence rates are a more useful way of trending results than focusing on the number of colonies recovered from a given sample. *Table 4* shows recommended incidence rates for aseptic processing environments. The incident rate is the rate at which environmental samples are found to contain any level of contamination. For example, an incident rate of 1% would mean that only 1% of the samples taken have any contamination regardless of colony number. In other words, 99% of the samples taken are completely free of contamination. Higher incidence rates than those recommended in *Table 4* may be acceptable in rooms of similar classification that are used for lower microbial risk activities. Action should be required when the incidence rate is seen to trend above these recommendations for a significant period of time.

Incidence rates should be based on actual monitoring data and should be retabulated regularly. Action levels should be based on actual empirical process capability. When contamination incidence rates are seen that exceed the recommendations in *Table 4* or are greater than established process capability, corrective actions should be taken. Corrective actions may include, but are not limited to, the following:

1. Revision of sanitization program including selection of antimicrobial agents, application methods, and frequencies.
2. Increased surveillance of personnel practices by supervisory staff. This may include written critiques of aseptic methods and techniques used by personnel.
3. Review of microbiological sampling methods and techniques.
4. When higher than typical glove and garment incidence levels are observed, additional training on gowning practices may be indicated.▲*USP29*

Change to read:

~~**Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms**~~

▲Methodology and Instrumentation for Sampling of Airborne Microorganisms▲*USP29*

~~It is generally accepted by scientists that airborne microorganisms in controlled environments can influence the microbiological quality of the intermediate or final products manufactured in these areas. Also, it generally is accepted that estimation of the airborne microorganisms can be affected by instruments and procedures used to perform these assays. Therefore, where alternative methods or equipment is used, the general equivalence of the results obtained should be ascertained. Advances in technology in the future are expected to bring innovations that would offer greater precision and sensitivity than the current available methodology and may justify a change in the absolute numbers of organisms that are detected.~~

▲TYPES OF SAMPLERS▲*USP29*

Today, the most commonly used samplers in the U.S. pharmaceutical and medical device industry are the impaction and centrifugal samplers. A number of commercially available samplers are listed for informational purposes. The selection, appropriateness, and adequacy of using any particular sampler is the responsibility of the user.

Slit-to-Agar Air Sampler (STA)—~~This sampler is the instrument upon which the microbial guidelines given in *Table 3* for the various controlled environments are based. The unit is powered by an attached source of controllable vacuum. The air intake is obtained through a standardized slit below which is placed a slowly revolving Petri dish containing a nutrient agar. Particles in the air that have sufficient mass impact on the agar surface and viable organisms are allowed to grow out. A remote air intake is often used to minimize disturbance of the laminar flow field.~~

▲The unit is powered by an attached source of controllable vacuum. The air intake is obtained through a standardized slit below which is placed a slowly revolving Petri dish containing a nutrient agar. Particles in the air that have sufficient mass impact on the agar surface and viable organisms are allowed to grow out. A remote air intake is often used to minimize disturbance of the unidirectional airflow field.▲*USP29*

Sieve ~~Impactor~~

▲Impaction▲*USP29*—The apparatus consists of a container designed to accommodate a Petri dish containing a nutrient agar. The cover of the unit is perforated, with the perforations of a predetermined size. A vacuum pump draws a known volume of air through the cover, and the particles in the air containing microorganisms impact on the agar medium in the Petri dish. Some samplers are available with a cascaded series of containers containing perforations of decreasing size. These units allow for the determination of the distribution of the size ranges of particulates containing viable microorganisms, on the basis of which size perforations admit the particles onto the agar plates.

Centrifugal Sampler—The unit consists of a propeller or turbine that pulls a known volume of air into the unit and then propels the air outward to impact on a tangentially placed nutrient agar strip set on a flexible plastic base.

Sterilizable Microbiological Atrium—The unit is a variant of the single-stage sieve impactor. The unit's cover contains uniformly spaced orifices approximately 0.25 inch in size. The base of the unit accommodates one Petri dish containing a nutrient agar. A vacuum pump controls the movement of air through the unit, and a multiple-unit control center as well as a remote sampling probe are available.

Surface Air System Sampler—This integrated unit consists of an entry section that accommodates an agar contact plate. Immediately behind the contact plate is a motor and turbine that pulls air through the unit's perforated cover over the agar contact plate and beyond the motor, where it is exhausted. Multiple mounted assemblies are also available.

Gelatin Filter Sampler—The unit consists of a vacuum pump with an extension hose terminating in a filter holder that can be located remotely in the critical space. The filter consists of random fibers of gelatin capable of retaining airborne microorganisms. After a specified exposure time, the filter is aseptically removed and dissolved in an appropriate diluent and then plated on an appropriate agar medium to estimate its microbial content.

Settling Plates—~~This method is still widely used as a simple and inexpensive way to~~ **qualitatively** assess the environments over ~~prolonged exposure times. The exposure of open agar-filled Petri dishes, or settling plates, is~~ **not to be used for quantitative** ~~estimations of the microbial contamination levels of critical environments.~~

~~One of the major limitations of mechanical air samplers is the limitation in sample size of air being sampled. Where the microbial level in the air of a controlled environment is expected to contain~~

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~~not more than three cfu per cubic meter, several cubic meters of air should be tested if results are to be assigned a reasonable level of precision and accuracy. Often this is not practical. To show that microbial counts present in the environment are not increasing over time, it might be necessary to extend the time of sampling to determine if the time of sampling is a limiting factor or not. Typically, slit-to-agar samplers have an 80-liter-per-minute sampling capacity (the capacity of the surface air system is somewhat higher). If one cubic meter of air is tested, then it would require an exposure time of 15 minutes. It may be necessary to use sampling times in excess of 15 minutes to obtain a representative environmental sample. Although there are samplers reported to be capable of very high sampling volume rates, consideration in these situations should be given to the potential for disruption of the airflow patterns in any critical area or to the creation of a turbulence that could increase the probability of contamination.~~

~~For centrifugal air samplers, a number of earlier studies showed that the samples demonstrated a selectivity for larger particles. The use of this type of sampler may have resulted in higher airborne counts than the other types of air samplers because of that inherent selectivity.~~

~~When selecting a centrifugal sampler, the effect of the sampler on the linearity of the airflow in the controlled zone where it is placed for sampling should be taken into consideration. Regardless of the type of sampler used, the use of a remote probe requires determining that the extra tubing does not have an adverse effect on the viable airborne count. This effect should either be eliminated or, if this is not possible, a correction factor should be introduced in the reporting of results.~~

▲This method is a simple and inexpensive way to qualitatively assess the environments over prolonged exposure times. Settling plates may be particularly useful in critical areas, where the use of an active sampling device could be unduly intrusive and therefore a hazard to safe aseptic operation. However, settle plates may be less efficient for the collection of airborne viable contamination than active air sampling devices, even when long exposure times (4–5 hours) are used.

SAMPLE VOLUMES FOR ACTIVE AIR MONITORING

One of the major limitations of mechanical air samplers is the limitation in sample size of air being sampled. Where the microbial level in the air of a controlled environment is expected to contain extremely low levels of contamination per unit volume, at least one cubic meter of air should be tested in order to maximize sensitivity. Typically, slit-to-agar samplers have a sampling capacity of 80 L per minute (the capacity of the surface air system is somewhat higher). If one cubic meter of air is tested, then it would require an exposure time of 15 minutes. It may be necessary to use sampling times in excess of 15 minutes to obtain a representative environmental sample. Although there are samplers reported to be capable of very high sampling volume rates, consideration in these situations should be given to the potential for disruption of the airflow patterns in any critical area or to the creation of a turbulence that could increase the probability of contamination.

Users may wish to use remote sampling systems in order to minimize the potential for risk to the process resulting from the intervention by environmental samplers in critical zones. Regardless of the type of sampler used, it must be determined that the use of a remote probe with its extra tubing does not reduce the method's sensitivity to such an extent that the detection of low levels of contamination becomes unlikely or even impossible.▲*USP29*

Change to read:

Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments

Another component of the microbial environmental control program in controlled environments is surface sampling of equipment, facilities, and personnel gear used in these environments. The standardization of surface sampling methods and procedures has not been as widely addressed in the pharmaceutical industry as the standardization of air sampling procedures.[3] To minimize disruptions to critical operations, surface sampling is performed at the conclusion of operations. Surface sampling may be accomplished by the use of *contact plates* or by the *swabbing method*. Surface monitoring is generally performed on areas that come in contact with the product and on areas adjacent to those contact areas. Contact plates filled with nutrient agar are used when sampling regular or flat surfaces and are directly incubated at a time appropriate for a given incubation temperature for quantitation of viable counts. Specialized agar can be used for specific quantitation of fungi, spores, etc.

~~The swabbing method may be used for sampling of irregular surfaces, especially for equipment. Swabbing is used to supplement contact plates for regular surfaces. The swab is then placed in an appropriate diluent and the estimate of microbial count is done by plating of an appropriate aliquot on or in specified nutrient agar. The area to be swabbed is defined using a sterile template of appropriate size. In general, it is in the range of 24 to 30 cm^2. The microbial estimates are reported per contact plate or per swab.~~

▲The swabbing method may be used for sampling of irregular surfaces, especially for equipment. Swabbing can also be used for regular surfaces. The area to be swabbed may be

[3] The Sixteenth Edition of Standard Methods for the Examination of Dairy Products (the American Health Association) provides a section on surface sampling.

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defined using a sterile template of appropriate size. In general, the size is in the range of 24 to 30 cm^2. After collection of the sample, the swab is placed in an appropriate diluent and plated onto the desired nutrient agar. The microbial estimates are reported per contact plate or per swab. Swabbing and contact sampling are widely used methods and can be expected to yield similar recovery levels in most industrial applications. It is not necessary for each user to validate recovery because these are standard methods in the industry.

Surface monitoring is used as an environmental assessment tool in all types of classified environments. In Class 5 environments in which aseptic processing is done, surface monitoring is generally performed adjacent to those contact areas. The entire area in which the product and the containers and closures are exposed in aseptic processing is typically defined as the critical zone. Component hoppers and feed chutes that contact sterile surfaces on closures and filling needles may be tested for microbial contamination. Typically, these product contact surfaces are steam sterilized and aseptically assembled or decontaminated in situ. The ability of operators to perform these aseptic manipulations are demonstrated during process simulations or media fills. It is important to note that surface monitoring on surfaces that directly contact sterile parts or product, if monitored, should be done only at the conclusion of operations. Sampling during operations would require a dangerous process-line intervention that could, in and of itself, create a hazard to sterility assurance. Surface sampling is not a sterility test and should not be used in and of itself as a criterion for the release or rejection of product. Given the fact that these samples must be taken aseptically by personnel, it can never be established with certainty that any contamination that is recovered would have affected the product.▲*USP29*

Change to read:

Culture Media and Diluents Used for Sampling or ~~Quantitation~~

▲Estimation▲*USP29* of Microorganisms

~~The type of medium, liquid or solid, that is used for sampling or quantitation of microorganisms in controlled environments will depend on the procedure and equipment used. A commonly used all-purpose medium is Soybean–Casein Digest Agar when a solid medium is needed. Other media, liquid or solid, are listed below.~~

~~Liquid Media*~~	~~Solid Media*~~
~~Tryptone saline~~	~~Soybean–casein digest agar~~
~~Peptone water~~	~~Nutrient agar~~
~~Buffered saline~~	~~Tryptone glucose extract agar~~
~~Buffered gelatin~~	~~Lecithin agar~~
~~Enriched buffered gelatin~~	~~Brain heart infusion agar~~
~~Brain heart infusion~~	~~Contact plate agar~~
~~Soybean–casein medium~~	

~~* Liquid and solid media are sterilized using a validated process.~~

~~These media are commercially available in dehydrated form. They are also available in ready-to-use form. When disinfectants or antibiotics are used in the controlled area, consideration should be given to using media with appropriate inactivating agents.~~

~~Alternative media to those listed can be used provided that they are validated for the purpose intended.~~

▲The type of medium, i.e., liquid, or solid, that is used for sampling or plating of microorganisms in controlled environments will depend on the procedure and equipment used. Any medium used must be validated for the intended purpose. When a solid medium is needed, a commonly used all-purpose microbiologial growth medium is Soybean–Casein Digest Agar.▲*USP29*

Change to read:

Identification of Microbial Isolates from the Environmental Control Program

~~The environmental control program includes an appropriate level of identification of the flora obtained from sampling. A knowledge of the normal flora in controlled environments aids in determining the usual microbial flora anticipated for the facility being monitored; evaluating the effectiveness of the cleaning and sanitization procedures, methods, and agents; and recovery methods. The information gathered by an identification program can also be useful in the investigation of the source of contamination, especially when the *Action levels* are exceeded.~~

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▲The environmental control program includes an appropriate level of identification of the flora obtained from sampling. A knowledge of the flora in controlled environments aids in the following: determining the usual microbial flora anticipated for the facility being monitored; evaluating the effectiveness of the cleaning and sanitization procedures, methods, and agents; and recovery methods. The information gathered by an identification program can also be useful in the investigation of the source of contamination, especially when recommended contamination incidence rates are exceeded, a situation that implies that corrective action is required.▲*USP29*

Identification of isolates from critical areas and areas immediate to these critical areas should take precedence over identification of microorganisms from noncritical areas. Identification methods should be verified, and ready-to-use kits should be qualified for their intended purpose (see *Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program*).

Add the following:

▲Conclusion

Environmental monitoring is one of several key elements required to ensure that a classified clean room or aseptic processing area is maintained with an adequate level of control. Monitoring is a qualitative exercise and even in the most critical applications such as aseptic processing, conclusions regarding lot acceptability should not be reached on the basis of environmental sampling results alone. Environments that are essentially free of human operators will generally have a very low initial contamination rate and will maintain very low levels of microbial contamination in use. However, human scale clean rooms present a vastly different picture. Studies conclusively show that operators continuously slough microorganisms into the environment, even when carefully and correctly gowned. Therefore, it is unreasonable to assume that recovery levels of zero, even in the critical zone or on critical surfaces, will be observed at all times. Periodic excursions are a fact of life in human scale clean rooms; however the incidence rate of contamination particularly in ISO Class 5 environments used for aseptic processing should be consistently low.

Clean room operators, particularly those engaged in aseptic processing must always strive to maintain a suitable quality of environment and must work towards continuous improvement of personnel operations and environmental control. In general, reductions in personnel involved in aseptic processing and monitoring and reduction in interventions will reduce the risk of microbial contamination.▲*USP29*

Delete the following:

~~▲Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments~~

~~The controlled environment is monitored through an appropriate environmental monitoring program. To assure that minimal bioburden is achieved, additional information on the evaluation of the microbiological status of the controlled environment can be obtained by the use of *media fills*. An acceptable media fill shows that a successful simulated product run can be conducted on the manufacturing line at that point in time. However, other factors are important, such as appropriate construction of facilities, environmental monitoring and training of personnel.~~

~~When an aseptic process is developed and installed, it is generally necessary to qualify the microbiological status of the process by running at least three successful consecutive media fills. A media fill utilizes growth medium in lieu of products to detect the growth of microorganisms. Issues in the development of a media fill program that should be considered are the following: media fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.~~

~~Since a media fill is designed to simulate aseptic processing of a specified product, it is important that conditions during a normal product run are in effect during the media fill. This includes the full complement of personnel and all the processing steps and materials that constitute a normal production run. During the conduct of media fill, various predocumented interventions that are known to occur during actual product runs should be planned (e.g., changing filling needles, fixing component jams).~~

~~Alternatively, in order to add a safety margin, a combination of possible conditions can be used. Examples may include frequent start and stop sequences, unexpected repair of processing system, replacement of filters, etc. The qualification of an aseptic process need not be done for every product, but should be done for each processing line. Since the geometry of the container (size as well as opening of the container) and the speed of the line are factors that are variable in the use of an aseptic processing line, appropriate combination of these factors, preferably at the extremes, should be used in the qualification of the line. A rationale for products used should be documented.~~

~~The 1987 FDA Guideline on Sterile Drug Products Produced by Aseptic Processing indicates that media fill runs be done to cover all production shifts for line/product/container combinations. This guideline should be considered not only for qualification media fill~~

runs, but also for periodic reevaluation or revalidation. Media fill programs should also simulate production practices over extended runs. This can be accomplished by doing media-fill runs at the end of production runs.

In general, an all-purpose, rich medium such as Soybean–Casein Broth that has been checked for growth promotion with a battery of indicator organisms (see *Sterility Tests* ⟨71⟩) at a level of below 100 cfu/unit, can be used. Isolates from the controlled environment where aseptic processing is to be conducted may also be used. Following the aseptic processing of the medium, the filled containers are incubated at 22.5 ± 2.5° or at 32.5 ± 2.5°. All media-filled containers should be incubated for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, then these filled containers should be incubated for at least 7 days at each temperature. Following incubation, the medium-filled containers should be inspected for growth. Media-filled isolates are identified by genus and, when possible, by species in order to investigate the sources of contamination.

Critical issues in performing media fills are the number of fills to qualify an aseptic process, the number of units filled per media fill, the interpretation of results, and implementation of corrective actions. Historically, three media-fill runs during initial qualification or start-up of a facility are conducted to demonstrate consistency of the aseptic processing line. The minimum number of units to demonstrate a contamination rate of not more than 0.1%, which is the criterion for acceptance of a successful media-fill run, is at least 3,000. It should be emphasized that many firms in the United States and other countries are filling more than 3,000 units in a single media-fill run.[4] Pilot plant facilities used for preparing small clinical lots may use smaller media fills.

A number of international documents (i.e., ISO and EU GMP) have also cited an expectation of zero positives out of 3,000 media filled units at the 95% confidence level. However, it is recognized that repeated media runs are required in order to confirm the statistical validity of the observed contamination rate for the process.

PDA Technical Monograph Number 17,[4] "A Survey of Current Sterile Manufacturing Practices," indicated that many manufacturers believe that their aseptic processes are capable of contamination rates below 0.1%.

Since the most critical source of contamination in the clean room is the personnel, visual documentation that can be helpful in correlating production activities to contamination events during media fills is encouraged. The widespread use of isolator systems for sterility testing has demonstrated that elimination of personnel does reduce contamination in aseptic handling. ▲*USP29*

Delete the following:

▲An Overview of the Emerging Technologies for Advanced Aseptic Processing

Because of the strong correlation between human involvement and intervention and the potential for product contamination in aseptic processing, production systems in which personnel are removed from critical zones have been designed and implemented. Methods developed to reduce the likelihood of contamination include equipment automation, barriers, and isolator systems. Facilities that employ these advanced aseptic processing strategies are already in operation. In facilities where personnel have been completely excluded from the critical zone, the necessity for room classification based on particulate and environmental microbiological monitoring requirements may be significantly reduced.

The following are definitions of some of the systems currently in place to reduce the contamination rate in aseptic processing:

Barriers— In the context of aseptic processing systems, a barrier is a device that restricts contact between operators and the aseptic field enclosed within the barrier. These systems are used in hospital pharmacies, laboratories, and animal care facilities, as well as in aseptic filling. Barriers may not be sterilized and do not always have transfer systems that allow passage of materials into or out of the system without exposure to the surrounding environment. Barriers range from plastic curtains around the critical production zones to rigid enclosures found on modern aseptic filling equipment. Barriers may also incorporate such elements as glove ports, half-suits, and rapid-transfer ports.

Blow/Fill/Seal— This type of system combines the blow-molding of container with the filling of product and a sealing operation in one piece of equipment. From a microbiological point of view, the sequence of forming the container, filling with sterile product, and formation and application of the seal are achieved aseptically in an uninterrupted operation with minimal exposure to the environment. These systems have been in existence for about 30 years and have demonstrated the capability of achieving contamination rates below 0.1%. Contamination rates of 0.001% have been cited for blow/fill/seal systems when combined media-fill data are summarized and analyzed.

Isolator— This technology is used for a dual purpose. One is to protect the product from contamination from the environment, including personnel, during filling and closing, and the other is to protect personnel from deleterious or toxic products that are being manufactured.

Isolator technology is based on the principle of placing previously sterilized components (containers/products/closures) into a sterile environment. These components remain sterile during the whole processing operation, since no personnel or nonsterile components are brought into the isolator. The isolator barrier is an absolute barrier that does not allow for interchanges between the protected and unprotected environments. Isolators either may be physically sealed against the entry of external contamination or may be effectively sealed by the application of continuous overpressure. Manipulations of materials by personnel are done via use of gloves, half-suits, or full-suits. All air entering the isolator passes through either an HEPA or ULPA filter, and exhaust air typically exits through an HEPA-grade filter. Peracetic acid and hydrogen peroxide vapor are commonly used for the surface sterilization of the isolator unit's internal environment. The sterilization of the interior of isolators and all contents are usually validated to a sterility assurance level of 10^{-6}.

Equipment, components, and materials are introduced into the isolator through a number of different procedures: use of a double-door autoclave; continuous introduction of components via a conveyor belt passing through a sterilizing tunnel; use of a transfer container system through a docking system in the isolator enclosure. It is also necessary to monitor closely an isolator unit's integrity, calibration, and maintenance.

The requirements for controlled environments surrounding these newer technologies for aseptic processing depend on the type of technology used.

Blow/Fill/Seal equipment that restricts employee contact with the product may be placed in a controlled environment, especially if some form of employee intervention is possible during production.

Barrier systems will require some form of controlled environment. Because of the numerous barrier system types and applications, the requirements for the environment surrounding the barrier system will vary. The design and operating strategies for the environment around these systems will have to be developed by the manufacturers in a logical and rational fashion. Regardless of these strategies, the capability of the system to produce sterile products must be validated to operate in accordance with pre-established criteria.

In isolators, the air enters the isolator through integral filters of HEPA quality or better, and their interiors are sterilized typically to a sterility assurance level of 10^{-6}; therefore, isolators contain sterile

[4] A Parenteral Drug Association Survey (Technical Monograph 17) showed that out of 27 respondents, 50% were filling more than 3,000 units per run.

~~air, do not exchange air with the surrounding environment, and are free of human operators. However, it has been suggested that when the isolator is in a controlled environment, the potential for contaminated product is reduced in the event of a pinhole leak in the suit or glove.~~

~~The extent and scope of an environmental microbiological monitoring of these advanced systems for aseptic processing depends on the type of system used. Manufacturers should balance the frequency of environmental sampling systems that require human intervention with the benefit accrued by the results of that monitoring. Since barrier systems are designed to reduce human intervention to a minimum, remote sampling systems should be used in lieu of personnel intervention. In general, once the validation establishes the effectiveness of the barrier system, the frequency of sampling to monitor the microbiological status of the aseptic processing area could be reduced, as compared to the frequency of sampling of classical aseptic processing systems.~~

~~Isolator systems require relatively infrequent microbiological monitoring. Continuous total particulate monitoring can provide assurance that the air filtration system within the isolator is working properly. The methods for quantitative microbiological air sampling described in this chapter may not have sufficient sensitivity to test the environment inside an isolator. Experience with isolators indicates that under normal operations pinhole leaks or tears in gloves represent the major potential for microbiological contamination; therefore, frequent testing of the gloves for integrity and surface monitoring of the gloves is essential. Surface monitoring within the isolator may also be beneficial on an infrequent basis.~~ ▲*USP29*

Change to read:

GLOSSARY

~~**Airborne Particulate Count** (also referred to as *Total Particulate Count*) — Particles detected are 0.5 µm and larger. When a number of particles is specified, it is the maximum allowable number of particles per cubic meter of air (or per cubic foot of air).~~

~~**Airborne Viable Particulate Count** (also referred to as *Total Airborne Aerobic Microbial Count*) — When a number of microorganisms is specified, it is the maximum number of colony-forming units (cfu) per cubic meter of air (or per cubic foot of air) that is associated with a Cleanliness Class of controlled environment based on the *Airborne Particulate Count*.~~

~~**Aseptic Processing** — A mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers/closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiologic critically controlled conditions.~~

~~**Air Sampler** — Devices or equipment used to sample a measured amount of air in a specified time to quantitate the particulate or microbiological status of air in the controlled environment.~~

~~**Air Changes** — The frequency per unit of time (minutes, hours, etc.) that the air within a controlled environment is replaced. The air can be recirculated partially or totally replaced.~~

~~**Action Levels** — Microbiological levels in the controlled environment, specified in the standard operating procedures, which when exceeded should trigger an investigation and a corrective action based on the investigation.~~

~~**Alert Levels** — Microbial levels, specified in the standard operating procedures, which when exceeded should result in an investigation to ensure that the process is still within control. Alert levels are specific for a given facility and are established on the basis of a baseline developed under an environmental monitoring program. These Alert levels can be modified depending on the trend analysis done in the monitoring program. Alert levels are always lower than Action levels.~~

~~**Bioburden** — Total number of microorganisms detected in or on an article.~~

~~**Clean Room** — A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate Cleanliness Class. In addition, the concentration of microorganisms in the environment is monitored; each Cleanliness Class defined is also assigned a microbial level for air, surface, and personnel gear.~~

~~**Clean Zone** — A defined space in which the concentration of airborne particles and microorganisms are controlled to meet specific Cleanliness Class levels.~~

~~**Controlled Environment** — Any area in an aseptic process system for which airborne particulate and microorganism levels are controlled to specific levels, appropriate to the activities conducted within that environment.~~

~~**Commissioning of a Controlled Environment** — Certification by engineering and quality control that the environment has been built according to the specifications of the desired cleanliness class and that, under conditions likely to be encountered under normal operating conditions (or worst-case conditions), it is capable of delivering an aseptic process. Commissioning includes media-fill runs and results of the environmental monitoring program.~~

~~**Corrective Action** — Actions to be performed that are in standard operating procedures and that are triggered when certain conditions are exceeded.~~

~~**Environmental Isolates** — Microorganisms that have been isolated from the environmental monitoring program.~~

~~**Environmental Monitoring Program** — Documented program, implemented through standard operating procedures, that describes in detail the procedures and methods used for monitoring particulates as well as microorganisms in controlled environments (air, surface, personnel gear). The program includes sampling sites, frequency of sampling, and investigative and corrective actions that should be followed if Alert or Action levels are exceeded. The methodology used for trend analysis is also described.~~

~~**Equipment Layout** — Graphical representation of an aseptic processing system that denotes the relationship between and among equipment and personnel. This layout is used in the *Risk Assessment Analysis* to determine sampling site and frequency of sampling based on potential for microbiological contamination of the product/container/closure system. Changes must be assessed by responsible managers, since unauthorized changes in the layout for equipment or personnel stations could result in increase in the potential for contamination of the product/container/closure system.~~

~~**Federal Standard 209E** — "Airborne Particulate Cleanliness Classes in Clean Rooms and Clean Zones" is a standard approved by the Commissioner, Federal Supply Services, General Service Administration, for the use of "All Federal Agencies." The Standard establishes classes of air cleanliness based on specified concentration of airborne particulates. These classes of air cleanliness have been developed, in general, for the electronic industry "superclean" controlled environments. In the pharmaceutical industry, the Federal Standard 209E is used to specify the construction of controlled environment. Class 100, Class 10,000, and Class 100,000 are generally represented in an aseptic processing system. If the classification system is applied on the basis of particles equal to or greater than 0.5 µm, these classes are now represented in the SI system by Class M3.5, M5.5, and M6.5, respectively.~~

~~**Filter Integrity** — Testing that ensures that a filter functional performance is satisfactory [e.g., dioctyl phthalate (DOP) and bubble point test].~~

~~**Material Flow** — The flow of material and personnel entering controlled environments should follow a specified and documented pathway that has been chosen to reduce or minimize the potential for microbial contamination of the product/closure/container systems. Deviation from the prescribed flow could result in increase in potential for microbial contamination. Material/personnel flow can be changed, but the consequences of the changes from a microbiological point of view should be assessed by responsible managers and must be authorized and documented.~~

~~**Media Growth Promotion**—Procedure that references *Growth Promotion* under *Sterility Tests* ⟨71⟩ to demonstrate that media used in the microbiological environmental monitoring program, or in *media-fill* runs, are capable of supporting growth of indicator microorganisms and of environmental isolates from samples obtained through the monitoring program or their corresponding ATCC strains.~~

~~**Media Fill**—Microbiological simulation of an aseptic process by the use of growth media processed in a manner similar to the processing of the product and with the same container/closure system being used.~~

~~**Out-of-Specification Event**—Temporary or continuous event when one or more of the requirements included in standard operating procedures for controlled environments are not fulfilled.~~

~~**Product Contact Areas**—Areas and surfaces in a controlled environment that are in direct contact with either products, containers, or closures and the microbiological status of which can result in potential microbial contamination of the product/container/closure system. Once identified, these areas should be tested more frequently than non-product contact areas or surfaces.~~

~~**Risk Assessment Analysis**—Analysis of the identification of contamination potentials in controlled environments that establish priorities in terms of severity and frequency and that will develop methods and procedures that will eliminate, reduce, minimize, or mitigate their potential for microbial contamination of the product/container/closure system.~~

~~**Sampling Plan**—A documented plan that describes the procedures and methods for sampling a controlled environment; identifies the sampling sites, the sampling frequency, and number of samples; and describes the method of analysis and how to interpret the results.~~

~~**Sampling Sites**—Documented geographical location, within a controlled environment, where sampling for microbiological evaluation is taken. In general, sampling sites are selected because of their potential for product/container/closure contacts.~~

~~**Standard Operating Procedures**—Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place in a controlled environment and auxiliary environments. Deviations from standard operating procedures should be noted and approved by responsible managers.~~

~~**Sterile Field**—In aseptic processing or in other controlled environments, it is the space at the level of or above open product containers, closures, or product itself, where the potential for microbial contamination is highest.~~

~~**Sterility**—Within the strictest definition of sterility, an article is deemed sterile when there is complete absence of viable microorganisms. Absolute sterility cannot be practically demonstrated without testing every article in a batch. Sterility is defined in probabilistic terms, where the likelihood of a contaminated article is acceptably remote.~~

~~**Swabs**—Devices provided that are used to sample irregular as well as regular surfaces for determination of microbial status. The swab, generally composed of a stick with an absorbent extremity, is moistened before sampling and used to sample a specified unit area of a surface. The swab is then rinsed in sterile saline or other suitable menstruum and the contents plated on nutrient agar plates to obtain an estimate of the viable microbial load on that surface.~~

~~**Trend Analysis**—Data from a routine microbial environmental monitoring program that can be related to time, shift, facility, etc. This information is periodically evaluated to establish the status or pattern of that program to ascertain whether it is under adequate control. A trend analysis is used to facilitate decision making for requalification of a controlled environment or for maintenance and sanitization schedules.~~

▲**AIRBORNE PARTICULATE COUNT** (also referred to as *Total Particulate Count*)—Particles detected are 0.5 µm and larger. When a number of particles is specified, that number refers to the maximum allowable number of particles of a specified size per cubic meter of air.

AIRBORNE VIABLE PARTICULATE COUNT (also referred to as *Total Airborne Aerobic Microbial Count*)—When a number of microorganisms is specified, that number refers to the maximum number of colony forming units (cfu) per cubic meter of air that is associated with a cleanliness class of controlled environment based on the *Airborne Particulate Count*.

ASEPTIC PROCESSING—Aseptic means the absence of pathogenic microorganisms. In the healthcare industry, aseptic processing is a mode of processing that involves the separate sterilization of the product and of the package (containers/closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiological, critically controlled conditions.

AIR SAMPLER—This is a device or equipment used to sample a measured amount of air in a specified time to evaluate the particulate or microbiological air quality in an environment.

AIR CHANGES—The frequency per unit of time (minutes, hours, etc.) with which the air within a controlled environment is replaced. The air can be recirculated partially or totally replaced.

ACTION LEVELS—These are incident rates that exceed those that are normally observed in an environment.

ASEPTIC—Technically, this term means the absence of pathogenic organisms; in the field of aseptic processing, however, "aseptic" refers to methods and operations that minimize microbial contamination in environments where filtered sterilized product and sterilized components are filled and/or assembled.

In-Process Revision

BIOBURDEN—Total number of microorganisms and identity of the predominant microorganisms detected in or on an article.

CLEAN ROOM—A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. In addition, the concentration of microorganisms in the environment is monitored; each cleanliness class defined is also assigned a microbial level for air, surface, and personnel gear.

CLEAN ZONE—A defined space in which the concentration of airborne particles and microorganisms are controlled to meet specific cleanliness class levels.

CONTROLLED ENVIRONMENT—Any area in an aseptic process system for which airborne particulate and microorganism levels are controlled to specific levels that are appropriate to the activities conducted within that environment.

COMMISSIONING OF A CONTROLLED ENVIRONMENT—Certification by engineering and by quality control that the environment has been built according to the specifications of the desired cleanliness class and that, under conditions likely to be encountered under normal operating conditions (or worst-case conditions), that environment is capable of delivering an aseptic process. Commissioning includes media-fill runs and results of the environmental monitoring program.

CORRECTIVE ACTION—Actions to be performed that are in standard operating procedures and that are triggered when certain conditions are exceeded.

CRITICAL ZONE—The entire area in which the product and the containers and closures are exposed in aseptic processing is typically defined as the critical zone.

ENVIRONMENTAL ISOLATES—Microorganisms that have been isolated from the environmental monitoring program.

ENVIRONMENTAL MONITORING PROGRAM—Documented program, implemented through standard operating procedures, that describes in detail the procedures and methods used for monitoring particulates as well as microorganisms in controlled environments (air, surface, personnel gear). The program includes sampling sites, frequency of sampling, and investigative and corrective actions that should be followed if alert or action levels are exceeded. The methodology used for trend analysis is also described.

EQUIPMENT LAYOUT—Graphical representation of an aseptic processing system that denotes the relationship between and among equipment and personnel. This layout is used in the *Risk Assessment Analysis* to determine sampling site and frequency of sampling based on the potential for microbiological contamination of the product/container/closure system. Changes must be assessed by responsible managers because unauthorized changes in the layout for equipment or personnel stations could result in an increase in the potential for contamination of the product/container/closure system.

INCIDENT RATES—The rate or frequency at which contamination is observed in an environment. Typically expressed as a percentage of samples in which contamination is observed per unit time.

ISO 14644—The international standard that has supplanted Federal Standard 209E and which defines cleanliness grades for clean rooms and recommends practices for the classification of these clean rooms in terms of their ability to control total particulate contamination.

MATERIAL FLOW—The flow of material and personnel entering controlled environments should follow a specified and documented pathway that has been chosen to reduce or minimize the potential for microbial contamination of the product/closure/container systems. Deviation from the prescribed flow could result in an increase in the

potential for microbial contamination. Material/personnel flow can be changed, but, from a microbiological point of view, the consequences of the changes should be assessed by responsible managers and must be authorized and documented.

MEDIA GROWTH PROMOTION—A procedure that references *Growth Promotion Test of Aerobes, Anaerobes, and Fungi* under *Sterility Tests* ⟨71⟩ to demonstrate that media used in the microbiological environmental monitoring program, or in media-fill runs, are capable of supporting growth of indicator microorganisms and of environmental isolates from samples obtained through the monitoring program or their corresponding ATCC strains.

MEDIA FILL—A microbiological simulation of an aseptic process by the use of growth media processed in a manner similar to the processing of the product and with the same container/closure system being used.

OUT-OF-TREND EVENT—A temporary or continuous event when one or more of the requirements included in the standard operating procedures for controlled environments are not fulfilled.

PRODUCT CONTACT AREAS—Areas and surfaces in a controlled environment that are in direct contact with either products, containers, or closures and the microbiological status of which can result in potential microbial contamination of the product/container/closure system.

RISK ASSESSMENT ANALYSIS—Analysis of the identification of contamination potentials in controlled environments that establishes priorities in terms of severity and frequency and that develops methods and procedures that will eliminate, reduce, minimize, or mitigate the potential for microbial contamination of the product/container/closure system.

SAMPLING PLAN—A documented plan that (1) describes the procedures and methods for sampling a controlled environment; (2) identifies the sampling sites, the sampling frequency, and number of samples; and (3) describes the method of analysis and how to interpret the results.

SAMPLING SITES—A documented geographical location, within a controlled environment, where sampling for microbiological evaluation is taken. In general, sampling sites are selected because of their potential for product/container/closure contacts.

STANDARD OPERATING PROCEDURES—Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place in a controlled environment and auxiliary environments. Deviations from standard operating procedures should be noted and approved by responsible managers.

STERILE OR ASEPTIC FIELD—The space at the level of or above open product containers used in aseptic processing or in other controlled environments.

STERILITY—Within the strictest definition of sterility, an article is deemed sterile when there is complete absence of viable microorganisms, where viability is defined as organisms having the capacity to reproduce. Absolute sterility cannot be practically demonstrated, as it is technically unfeasible to prove a negative absolute.

SWABS—Devices that are used to sample irregular as well as regular surfaces for determination of microbial status. The swab, generally composed of a stick with an absorbent extremity, is moistened before sampling and used to sample a specified unit area of a surface. The swab is then rinsed in sterile saline or other suitable menstruum and the contents plated on nutrient agar plates to obtain an estimate of the viable microbial load on that surface.

TREND ANALYSIS—Data from a routine microbial environmental monitoring program that can be related to time, shift, facility, etc. This information is periodically evaluated to establish the status or pattern of that program to ascertain whether it is under adequate control. A trend analysis is used to facilitate decision-making for requalification of a controlled environment or for maintenance and sanitization schedules.▲*USP29*

BRIEFING

⟨1225⟩ Validation of Compendial Methods, *USP 28* page 2748 and page 1382 of *PF* 30(4) [July–Aug. 2004]. On the basis of comments received, it is proposed to delete the section on *Ruggedness* because this concept is described under *Precision* as ''intermediate precision.'' The term ''pharmaceutical products'' is replaced with ''pharmaceutical articles'' to indicate that this chapter applies to both drug substances and drug products (see the USP *General Notices*). It is also indicated, in *Robustness,* that robustness may be investigated during method development. In previous revisions, the term ''method(s)'' was replaced with ''procedure(s)'' to align with the terms used by the International Conference on Harmonization (ICH). Even though these terms have different meanings throughout USP, it is expected that USP will continue to make this change, where appropriate, in order to harmonize with ICH terminology.

(PA4: H. Pappa) RTS—41909-1; 42042-2; 42077-1; 42149-1; 42162-1

Change to read:

⟨1225⟩ VALIDATION OF COMPENDIAL ~~METHODS~~

▲PROCEDURES▲*USP29*

Change to read:

Test procedures for assessment of the quality levels of pharmaceutical ~~products~~

▲articles▲*USP29*
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~~

▲articles▲*USP29*
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 *USP–NF* are not required to validate the accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use. Recognizing the legal status of *USP* and *NF* standards, it is essential, therefore, that proposals for adoption of new or revised compendial analytical ~~methods~~

▲procedures▲*USP29*
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 dealt with only 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.*~~

▲▲*USP29*

Change to read:

SUBMISSIONS TO THE COMPENDIA

Submissions to the compendia for new or revised analytical ~~methods~~

▲procedures▲*USP29*
should contain sufficient information to enable members of the ~~USP Committee of Revision~~

▲USP Council of Experts and its Expert Committees▲*USP29*
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,▲*USP29*
determination of the need for the ~~methods,~~

▲procedures,▲*USP29*
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▲*USP29*
and describe the capability of the specific ~~method~~

▲procedure▲*USP29*
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▲*USP29*

and advantages offered by the proposed ~~method.~~

▲procedure.▲*USP29*

Proposed Analytical Procedure—This section should contain a complete description of the analytical ~~method~~

▲procedure▲*USP29*
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 system 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.▲*USP29*
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▲*USP29*
is the process by which it is established, by laboratory studies, that the performance characteristics of the ~~method~~

▲procedure▲*USP29*
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▲*USP29*
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
▲Robustness▲*USP29*
~~Ruggedness~~

In the case of compendial ~~methods,~~

▲procedures,▲*USP29*
revalidation may be necessary in the following cases: a submission to the USP of a revised analytical ~~method;~~

▲procedure;▲*USP29*
or the use of an established general ~~method~~

▲procedure▲*USP29*
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▲*USP29*
is the closeness of test results obtained by that ~~method~~

▲procedure▲*USP29*
to the true value. The accuracy of an analytical ~~method~~

▲procedure▲*USP29*
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▲*USP29*
to an analyte of known purity (e.g., a Reference Standard) or by comparison of the results of the ~~method~~

▲procedure▲*USP29*
with those of a second, well-characterized ~~method;~~

▲procedure,▲*USP29*
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▲*USP29*
to synthetic mixtures of the drug product components to which known amounts of analyte have been added within the range of the ~~method.~~

▲procedure.▲*USP29*
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,▲*USP29*
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.▲*USP29*
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

▲(relative▲*USP29*
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.

In-Process Revision

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.▲*USP29*

PRECISION

Definition—The precision of an analytical ~~method~~

▲procedure▲*USP29*
is the degree of agreement among individual test results when the ~~method~~

▲procedure▲*USP29*
is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical ~~method~~

▲procedure▲*USP29*
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▲*USP29*
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

▲(also known as ruggedness)▲*USP29*
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.~~

▲▲*USP29*

Determination—The precision of an analytical ~~method~~

▲procedure▲*USP29*
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 (coefficient 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)▲*USP29*
have preferred the term "selectivity," reserving "specificity" for those procedures that are completely selective.] For the ~~test or assay methods~~

▲tests discussed▲*USP29*
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).▲*USP29*

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▲*USP29*
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 *(USP28)*~~

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,▲*USP29*
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▲*USP29*
may be used as for noninstrumental

▲procedures.▲*USP29*
In the case of ~~methods~~

▲procedures▲*USP29*
submitted for consideration as official compendial ~~methods,~~

▲procedures,▲*USP29*
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 responses. 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,▲*USP29*
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▲*USP29*
may be used as for noninstrumental

▲procedures.▲*USP29*
In the case of ~~methods~~

▲procedures▲*USP29*
submitted for consideration as official compendial ~~methods,~~

▲procedures,▲*USP29*
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 that an analyte be assayed at the level of 0.1 mg per tablet, it should be demonstrated that the ~~method~~

▲procedure▲*USP29*
will reliably quantitate the analyte at that level.

In the case of instrumental analytical ~~methods~~

▲procedures▲*USP29*
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▲*USP29*
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▲*USP29*

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.▲*USP29*

Definition of Range—The range of an analytical ~~method~~

▲procedure▲*USP29*
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▲*USP29*
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.▲*USP29*

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.~~

▲▲*USP29*
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▲*USP29*
is validated by verifying that the analytical ~~method~~

▲procedure▲*USP29*
provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range.

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.▲*USP29*

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▲*USP29*
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.~~

~~**Determination**—The ruggedness of an analytical method is determined by analysis of aliquots from homogeneous lots, in different laboratories, 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.~~

▲▲*USP29*

ROBUSTNESS

Definition—The robustness of an analytical ~~method~~

▲procedure▲*USP29*
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▲*USP29*
during normal usage.

▲Robustness ~~should~~ may be determined during development of the analytical procedure.▲*USP29*

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.▲*USP29*
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~~

In-Process Revision

▲procedure▲*USP29*
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▲*USP29*
depend on the type of ~~method~~

▲procedure▲*USP29*
being evaluated. They are especially important in the case of chromatographic ~~methods, and submissions~~

▲procedures. Submissions▲*USP29*
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~~

▲▲*USP29*

Validation

Compendial ~~assay procedures~~

▲test requirements▲*USP29*
vary from highly exacting analytical determinations to subjective evaluation of attributes. Considering this ~~variety of assays,~~

▲broad variety,▲*USP29*
it is only logical that different test ~~methods~~

▲procedures▲*USP29*
require different validation schemes. This chapter covers only the most common categories of ~~assays~~

▲tests▲*USP29*
for which validation data should be required. These categories are as follows:

Category I—Analytical ~~methods~~

▲procedures▲*USP29*
for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

Category II—Analytical ~~methods~~

▲procedures▲*USP29*
for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These ~~methods~~

▲procedures▲*USP29*
include quantitative assays and limit tests.

Category III—Analytical ~~methods~~

▲procedures▲*USP29*
for determination of performance characteristics (e.g., dissolution, drug release).

Category IV—Identification tests.
For each ~~assay~~

▲▲*USP29*
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.▲*USP29*

Table 2. Data Elements Required for ~~Assay~~

▲▲*USP29*

Validation

Analytical Performance Characteristics	~~Assay~~ ▲▲*USP29* Category I	~~Assay~~ ▲▲*USP29* Category II: Quantitative	~~Assay~~ ▲▲*USP29* Category II: Limit Tests	~~Assay~~ ▲▲*USP29* Category III	~~Assay~~ ▲▲*USP29* Category IV
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~~▲▲*USP29*

* 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)▲*USP29*
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▲*USP29*
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▲*USP29*
is suitable for its intended application(s).

▲Current compendial procedures are also subject to regulations that require demonstration of suitability under actual conditions of use.▲*USP29*
Appropriate documentation should accompany any proposal for new or revised compendial analytical procedures.

BRIEFING

⟨**1226**⟩ **Verification of Compendial Procedures.** The purpose of this new general information chapter is to provide guidelines for verifying the suitability of a compendial procedure under actual conditions of use, as stated in 21 CFR 211.194(a)(2). Because it is not necessary for users of compendial procedures to perform a complete validation, but rather, to confirm that the procedure works for their drug substance, excipient, or dosage form, verification can be accomplished by assessing a subset of validation characteristics. This new chapter is considered an extension of the general information chapter *Validation of Compendial Methods* ⟨1225⟩, and both chapters use similar terminology. Interested parties are encouraged to submit comments by July 15, 2005.

(PA1: K. Russo) RTS—42133-1

Add the following:

▲⟨1226⟩ VERIFICATION OF COMPENDIAL PROCEDURES

Calibration, validation, and traceability are core metrological components. The validation of analytical procedures is a standard practice in pharmaceutical analytical laboratories because it ensures the accuracy and reliability of generated data. General information chapter *Validation of Compendial Methods* ⟨1225⟩ provides guidance on characteristics that should be evaluated for various test categories and on the documentation that should accompany analytical procedures submitted for inclusion in *USP–NF*. Chapter ⟨1225⟩ does not provide guidance on verifying the suitability of compendial procedures. The intent of general information chapter ⟨1226⟩ is to provide guidance to laboratories on how to verify that a compendial procedure that is being performed for the first time will yield acceptable results utilizing the laboratories' personnel, equipment, and reagents. Verification consists of assessing selected *Analytical Performance Characteristics,* which are described in chapter ⟨1225⟩, to generate appropriate, relevant data rather than repeating the validation process.

Users of compendial analytical procedures are not required to validate these procedures when first used in their laboratories, but suitability should be established under actual conditions of use. In the United States, this requirement is established in 21 CFR 211.194(a)(2), which states that "the suitability of all testing methods used shall be verified under actual conditions of use." In cases where multiple sites or laboratories will perform the monograph test for the first time, one laboratory may verify the suitability of the procedure, and then conduct a procedure transfer to the other locations.

Microbiological procedures are not included in this chapter because they are covered in USP general chapters *Antimicrobial Effectiveness Testing* ⟨51⟩, *Microbial Limit Tests* ⟨61⟩, *Sterility Tests* ⟨71⟩, and *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩.

VERIFICATION PROCESS

Laboratory personnel should have the appropriate experience, knowledge, and training to understand and be able to perform the compendial procedure as written. An approved document should be available prior to performing the com-

pendial procedure; this document describes the procedure to be verified, establishes the number and identity of lots or batches of articles that will be used in the verification test, details the analytical performance characteristics (see *Table 1*) to be evaluated, and specifies the range of results that will be considered acceptable. Any deviation from the recommendations in chapter ⟨1226⟩ should be justified in this documentation. Acceptance criteria should be established such that results meeting the requirements will provide confidence that the compendial procedure will perform suitably. Typically, the acceptance criteria would be more stringent than the compendial monograph specifications for the test.

Once the samples described in the verification document are analyzed, the data should be compared to the predetermined and approved acceptance criteria and the results documented. Documentation should include a summary of the analytical data, an assessment of the results and comparison to the acceptance criteria, and a conclusion as to the acceptability of the data as they relate to the ability of the laboratory analysts to successfully perform the compendial procedure in the particular laboratory. Once the results are shown to be acceptable, it can be concluded that the USP procedure will perform in the laboratory as intended.

If any of the acceptance criteria are not met, the source of the problem should be identified and corrective action, where appropriate, should be initiated (e.g., providing additional training for the laboratory analyst, or contacting USP staff for clarification of the procedure). Revisions to the verification document to include the implemented corrective actions should be made before the procedure is repeated. The initial unacceptable results, the most probable cause, and corrective actions implemented should be described in the final document.

If, after several attempts, the verification of the compendial procedure is not successful, and assistance from USP staff has not resolved the problem, it may be concluded that the procedure may not be suitable for use with the article being tested. It may then be necessary to develop and validate an alternate procedure and submit the data to USP with a recommendation to replace the current compendial procedure with the new procedure. In some situations it may be possible to revise the current procedure by adding the new procedure as an alternative to the current procedure.[1] The final internal verification documentation should summarize the inability to verify the compendial procedure and describe the action that was taken.

ANALYTICAL PERFORMANCE CHARACTERISTICS

The analytical performance characteristics that are typically included in the validation of procedures and that should be considered for the verification process are defined in general information chapter ⟨1225⟩.

Table 2 in chapter ⟨1225⟩ lists the analytical performance characteristics to be determined for several categories of assays to ensure that the procedure is validated. However, not all of the characteristics listed in chapter ⟨1225⟩, *Table 2,* need to be repeated for the verification of the compendial procedure in a laboratory. Depending on the type of test to be verified, different analytical performance characteristics should be studied.

Table 1 in this chapter includes examples of analytical performance characteristics that should be studied for various common analytical techniques applied to drug substances and excipients; corresponding information for dosage forms for each of the categories is presented in *Table 2* of this chapter. For several of the categories, the number of analytical performance characteristics to be studied for dosage forms is generally larger than that for excipients or drug sub-

[1] Request for revision includes both new monograph or general chapters and suggested changes to existing monographs and general chapters. See the USP *Guideline for Submitting Requests for Revision to the USP–NF.*

stances because of the greater complexity of a drug product. Where the technique is not suitable for the category, no data elements are displayed in the table.

In addition to the analytical performance characteristics summarized in *Table 1,* the evaluation of other characteristics may be considered in order to provide further assurance that the procedure will continue to perform as intended when unplanned changes occur in analysts, equipment, reagent, or environmental conditions, or when deliberate adjustments are made in procedure parameters. The sensitivity of the procedure to these changes can be measured by a robustness study. An appropriate ruggedness study may be necessary if there is a possibility that the procedure will be used by more than one analyst or if the procedure is to be transferred to multiple company sites or laboratories. The design of the ruggedness study will depend on how the procedure will be used. The definition of ruggedness and robustness can be found in chapter ⟨1225⟩. Verification is not required for general tests such as residue on ignition, unless there is a reason to suspect that the compendial procedure is not appropriate for the article under test.

Table 1. Data Elements for Verification of Drug Substances and Excipients

Technique	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
HPLC/GC	Precision	Precision Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Spectrophotometric/colorimetric	Precision	Precision Quantitation Limit	Specificity Detection Limit	—	Specificity
Titrimetric	Precision	Precision	—	—	—
TLC	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Gel Electrophoresis	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity

- *Category I:* Analytical procedures for quantitation of major components of drug substances or active ingredients (including preservatives) in finished dosage forms.
- *Category II:* Analytical procedures for determination of impurities in drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.
- *Category III:* Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release).
- *Category IV:* Identification procedures.

Table 2. Data Elements for Verification of Dosage Forms

Technique	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
HPLC/GC	Precision Specificity Linearity Range	Precision Specificity Quantitation Limit	Specificity Detection Limit	Precision	Specificity
Spectrophotometric/colorimetric	Precision Linearity Range	Precision Quantitation Limit	Specificity Detection Limit	Precision	Specificity
Titrimetric	Precision Linearity Range	Precision	—	—	—
TLC	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Gel Electrophoresis	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity

- *Category I:* Analytical procedures for quantitation of major components of drug substances or active ingredients (including preservatives) in finished dosage forms.
- *Category II:* Analytical procedures for determination of impurities in drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.
- *Category III:* Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release).
- *Category IV:* Identification procedures.▲*USP29*

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DIETARY SUPPLEMENTS

General Chapters—General Information

BRIEFING

⟨2030⟩ Supplemental Information for Articles of Botanical Origin. Quality control directly impacts the safety and efficacy of botanical products. Until now little attention has been given to the importance of good agricultural practices as the first step in the continuum of processes required in achieving consistent high quality botanical products and in reducing the adverse events associated with raw material of low quality including intentional and unintentional adulterants. This chapter contains information for specific botanicals about quality assurance measures for good agricultural and collection practices and other auxiliary information not covered in the monographs that is deemed to be important for achieving raw material of consistent quality.

(DSB: J. Salguero) RTS—41788-1

Add the following:

▲⟨2030⟩ SUPPLEMENTAL INFORMATION FOR ARTICLES OF BOTANICAL ORIGIN

This general chapter provides information about several aspects of botanical articles not covered in *USP* standards monographs. Although the standards in the monographs address the quality issues associated with botanical plant materials, extracts, and preparations of Pharmacopeial articles, there is a need to develop appropriate information to optimize the preharvesting conditions for appropriate growth and the postharvesting handling to achieve consistent quality with minimum variations in the composition of chemical constituents.

PROTOCOL CONTENTS

GENERAL GUIDANCES

It is recommened that, at a minimum, growers and others involved in the handling and distribution of botanical products should become familiar with and follow the WHO guidelines for good agricultural and collection practices for medicinal plants. Information about this document can be obtained at www.who.int/medicines/library/trm/medicinalplants/agricultural.shtml.

Commercial trade in natural products occurs in a global market. Material of domestic origin must be produced in compliance with all federal laws of the United States. Material of foreign origin, imported into the U.S., must be produced and transported in compliance with the laws of the U.S., the country of origin, and relevant international treaties. These include, but may not be limited to the following:

1. The Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) is an international agreement between governments. Its aim is to ensure that international trade in specimens of wild animals and plants does not threaten their survival. Information about CITES is available at http:/www.cites.org.
2. The Convention on Biological Diversity (CBD) establishes three main goals: the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of the benefits from the use of genetic resources. Each country that has ratified and is a party to the Convention is responsible for implementation by means of national enabling legislation that can differ from country to country.

3. The Endangered Species Act (ESA) was originally adopted in 1973. The ESA is a law that aims to protect species of fish, wildlife, and plants believed to be threatened with extinction. The ESA is administered primarily by the U.S. Fish and Wildlife Service. Full text of the act is available at: http://endangered.fws.gov/esa.html.

Provided below is additional information not covered in the compendial specifications: historical use; sources; collection and cultivation, including common adulterants; drying, storing, and shipping; and global regulatory status. This information is provided to complement the standards for quality control in the monographs for botanical articles.

ADDITIONAL INFORMATION FOR PROTOCOLS

Historical Use—The focus in this section is on historical compendial use that has strong validity, with only brief reference to anecdotal use. This is important information because traditional use is one of the elements taken into consideration to support the safety and the presumptions of benefits of botanical dietary supplements.

Sources—Included here is the point of origin of the botanical and encompasses cultivation (defined as agricultural growing) and wildcrafting (defined as collected in the wild), along with a listing of the primary geographical (native) areas of production.

Collection and Cultivation—This section discusses wildcrafting, the conservation of restricted and rare species, and the trend to cultivation as an ecological alternative; such optimal harvesting and collection practices serve to preserve the integrity of species and botanical products. It is subdivided into four subsections:

1. Collection (conservation and ecology)
2. Cultivation Practices
3. Optimal Times for Harvest
4. Optimal Handling and Processing Practices

Drying, Storage, and Shipping—Important factors regarding storage of herbal products and how they should be maintained include the following.

1. *Light:* Protection from light is particularly important for botanical articles. Light accelerates numerous chemical processes that may lead to degradation or changes in the constituents of the articles.
2. *Temperature:* Storage temperatures in this Pharmacopeia are defined in the *General Notices.* Excessive heat may affect the content of volatile constituents (essential oils) and accelerate degradation processes. However, heat treatments are sometimes useful in the maintenance of the article's quality and can be used in drying, killing microorganisms, and inhibiting certain enzymes. Heat application during these processes must be carefully controlled to achieve the desired balance between degradation and quality conservation.
3. *Humidity:* Moisture in the articles may allow certain enzymes such as glycosidases to become active, hence degrading constituents. High humidity also increases the danger of microbial proliferation. As a rule, it is advisable to store botanical articles below 60% relative humidity. Controlled humidity and temperature warehouses are now required in many good manufacturing practices for natural products.
4. *Degree of Comminution:* The degree of comminution plays a role in determining the stability of the botanical articles during storage. The increased surface area in fine powders allows oxidation and other degradation processes to occur more extensively and rapidly than in the case of a whole article. Plants containing tannins,

bitter substances, and essential oils are particularly sensitive to the degree of comminution, and therefore storage as a whole plant is preferred in these cases.

5. *Containers*—Appropriate containers are defined in this Pharmacopeia in the *General Notices.*

Constituents—Where known, the substances mainly responsible for the activity of the product are listed, along with other compounds contained in the plant.

Global Regulatory Status—The regulatory recognition of botanicals around the world changes constantly, so it is very difficult to provide comprehensive, up-to-date information for this section. Therefore, this section is limited to a list of countries in which a particular botanical is officially recognized.

GOOD AGRICULTURAL PRACTICE PROTOCOLS

Black Cohosh *Actaea racemosa* L. [*Cimicifuga racemosa* (L.) Nutt.] (Fam. Ranunculaceae)

Botanical Identification—*Actaea racemosa* L. Herbaceous perennial from rhizome.

Stem: Erect, solitary, to 2.5 m tall, glabrous.

Leaves: Basal and cauline, alternate, 2-4-ternately compound, petioles 15 to 60 cm long, bases clasping stem; leaflets 20 to 70; terminal leaflet of central division 3-lobed, 6 to 15 cm long, 6 to 16.5 cm wide, with 3 prominent veins arising from base; subterminal leaflets with blades ovate-lanceolate to obovate, 4 to 12 cm long and 3 to 8 cm wide; margins toothed to deeply incised; green above, paler below; glabrous or rarely pubescent along veins of undersurface.

Inflorescence: Terminal panicle of 4 to 9 slender branches, each 7 to 60 cm long, pubescent; 1 bract subtending each pedicel.

Flowers: Perfect, radially symmetric; sepals 4, greenish-white, caducous; petals 0; staminodes (1-) 4 (-8), petaloid, cream-colored, 2 to 3 mm long, clawed, apex bifid; stamens 55 to 110; pistils 1 (-3), glabrous to pubescent, ovary superior, style short, stigma 0.5 mm wide.

Fruit: Many-seeded follicle, 5 to 10 mm long, ovoid, laterally compressed with curved, stout beak (peristent style), pubescent; seeds hemispheric, brown, scales lacking. Chromosome number: n = 8.

There are currently two varieties of *A. racemosa* recognized based on differences in leaf morphology: var. *racemosa* and var. *dissecta*. The former variety has triternate-pinnate leaves with serrate margins, while the latter has quadriternate-pinnate leaves that are deeply incised with serrate lobes. Variety *dissecta* is only known from very few herbarium specimens, all of which were collected well over 100 years ago, making this taxon of uncertain taxonomic significance.

Historical Use—Black Cohosh appeared on the secondary list of substances in the first *United States Pharmacopeia (USP)* of 1820, where it was listed as an anti-inflammatory and antispasmodic. It soon rose to the primary list in 1830, a position it held until the 10th decennial revision of 1920. Black Cohosh appeared in the first edition of the *United States Dispensatory (USD)* in 1833 and remained through 1955 for a total of 122 years. Carrying forward the traditional Native American use of Black Cohosh for women's ailments and Barton's use for throat complaints, current therapeutics finds the plant used in a number of preparations for coughs and for gynecological disorders. In 2001, both the rhizome and the dry rhizome extract of Black Cohosh were proposed once again for inclusion in the *United States Pharmacopeia–National Formulary* (see revised proposal on page 1455 of *PF* 28(5) [Sept.–Oct. 2002].

Constituents—Major constituents of Black Cohosh are triterpene glycosides principally as beta-xylopyranosides and alpha-arabinopyranosides. The aglycones are mostly derived from acteol and cimigenol. The nomenclature of these compounds is quite confusing in the literature with different names often given to the same compounds. A cyclopropane ring is a common feature of these compounds, which are structurally related to cycloartenol. The isoflavone formononetin has been reported in some publications, however recent evidence indicates its absence in the roots and rhizomes of *Actaea racemosa.* Other constituents include tannins, resin, fatty acids, starch, sugars, and aromatic acids including ferulic acid, isoferulic acid, caffeic acid, and salicylic acid.

Sources—Black Cohosh can be found in moist deciduous forests, ravines, moist meadows, creek margins, and mountainous terrain. Black Cohosh flowers June to September and is native to eastern North America from Ontario south to Georgia and west to Missouri. The entire supply of Black Cohosh comes from the United States. The major producers of Black Cohosh are Kentucky and Tennessee, with additional supplies coming from Georgia, Ohio, North Carolina, Michigan, South Carolina, Virginia, West Virginia, and Wisconsin. Although there are reports of Black Cohosh being grown in China and India for export, the true identity of the cultivated material has not been verified and may well be an Asian species of *Actaea* such as *A. cimicifuga (syn. Cimicifuga foetida)*. The vast majority of the commercial Black Cohosh is wild harvested. Concern over the conservation of Black Cohosh due to increasing demand makes this species a good candidate for cultivation.

Collection and Cultivation—

*Collection (Conservation and Ecology)—*Traditionally, Black Cohosh has been harvested after plants become reproductive, which occurs anywhere from 2 to 8 years of age in cultivated plants depending on growing techniques (see *Cultivation*). A portion of the rhizome with a visible bud on it should be left in the ground to resprout the following year. There is no published information on the relationship between the constituent profile of the rhizome and its age, growing conditions, or place of origin, although such studies are underway. The impact of harvest on wild populations of Black Cohosh is currently unknown and sources differ in their opinion about it. While some maintain that current levels of harvest threaten the viability of wild populations, others feel that sustainable harvesting is possible at current levels of demand. A study of sustainable harvest limits is currently underway. The regulatory status regarding the trade of Black Cohosh is under review by the CITES. Refraining from harvesting plants until after they have set seed and leaving a portion of the rhizome in the ground to resprout are key components to sustainable harvesting.

*Cultivation Practices—*Black Cohosh is grown from rhizome cuttings or seeds and requires some shading, depending on altitude and other environmental conditions. If grown from rhizome cuttings, a plant takes 2 to 3 years to become reproductive; grown from seed sown in the greenhouse and then planted, takes 4 to 6 years; direct-seeded may take from 6 to 8 years. Preliminary work indicates that Black Cohosh can be propagated successfully using in vitro techniques.

*Optimal Times for Harvest—*Rhizomes and roots should be harvested in autumn when the plant is dormant. At that time the underground portions of the plant have lower moisture content than in other seasons. Fall harvesting also allows plants to produce mature seeds before being uprooted.

*Optimal Handling and Processing Practices—*Rhizomes with roots may be processed fresh or dried. They should be thoroughly washed directly after harvest and then laid out to dry. Freshly harvested roots should be solid but not woody.

Drying, Storage, and Shipping—

*Drying—*Rhizomes with roots are cut and air-dried at 35° to 45°. They are fully dried when they are brittle and snap easily and when no moisture is evident in cross section, either visibly or to the touch.

Storage—Follow general guidelines for storage by packing in airtight containers protected from light, heat, moisture, and insect infestation.

Adulterants—Other species of *Actaea,* especially yellow cohosh (*A. podocarpa* syn. *Cimicifuga americana*), have commonly but unintentionally been mixed with *A. racemosa* due to the similarity in above-ground appearance between species. The two species can be distinguished by differences in their freshly harvested underground parts: the fresh rhizome of *A. podocarpa* has a distinct yellowish hue, whereas that of *A. racemosa* is black. The rhizomes of both species are far more difficult to tell apart when dry because *A. podocarpa* darkens upon drying. The underground portions of baneberry *(Actaea pachypoda* and *A. rubra)* occur as occasional adulterants of Black Cohosh supplies. Fruiting plants of baneberry may be distinguished from Black Cohosh by their fleshy white or red poisonous berries, which contrast with the dry follicles of Black Cohosh. No information was available on how to distinguish the underground portions of Black Cohosh and baneberry from each other. According to one herb dealer, the roots of baneberry are smaller than those of Black Cohosh, and therefore are not often harvested by wildcrafters. In the Pacific Northwest, *Actaea elata* (syn. *Cimicifuga elata*) is collected for medicinal use.

There is no published information on chemical means of distinguishing the rhizomes of any of the above species. However, work using random amplified polymorphic DNA (RAPDs) to identify plant taxa both at and below the species level make it likely that such DNA testing would be useful in the identification of *Actaea* species. Investigators using RAPDs were able to distinguish Black Cohosh from other medicinal plant species. Various Asian species of *Actaea* are sold as Chinese Cimicifuga, including sheng ma (*A. cimicifuga* syn. *Cimicifuga foetida*), xing an sheng ma (*A. dahurica* syn. *C. dahurica*), and da san ye sheng ma (*A. heracleifolia* syn. *C. heracleifolia*; also known as guan sheng ma). Guang dong sheng ma, a member of the *Serratula* genus, is a common substitute for sheng ma in the Asian market. While these species are generally not found as adulterants of Black Cohosh, they are mentioned here due to similarities in medicinal use and the increasing overlap of the Asian and American herb markets.

Global Regulatory Status—

1. World Health Organization monograph published in 2003.
2. ESCOP monograph "Cimicifugae rhizoma" published in 2003.
3. *Austria:* The fresh or dried rhizome with attached roots is an approved nonprescription drug for oral use. Indications: Premenstrual disorders, dysmenorrhea, or climacteric [menopausal] neurovegetative ailments.
4. *Brazil:* Resolution n° 89/04 (ANVISA—simple register without clinical trials): Used part: roots or rizome; Markers: 27-deoxyactein or isoferulic acid; Use forms: extracts; Indications: climacteric symptoms; Dose: 1.8 mg per day of 27-deoxyacteine; Administration route: oral; Under prescription drug.
5. *Canada:* Black Cohosh will be listed as a Natural Health Product under new regulations if a health claim is made or if it is provided in specific dosage forms. Crude herbs in bulk form will remain regulated as "foods". When identified as a Traditional Herbal Medicine, Black Cohosh preparations are regulated as nonprescription OTC drugs requiring premarket registration and assignment of a drug identification number.
6. *France:* Official requirements for herbal remedies in France: French Agency for the safety of drugs (Agence Francaise de Sécurité Sanitaire des Produits de Santé, AFSSAPS), Notice to applicants for marketing authorization, Cahiers de l'Agence nr 3, 1999. Classement pharmaco-thérapeutique VIDAL: "Sdatif d'origine végétale".

7. *Germany:* The fresh or dried rhizome with attached roots is an approved nonprescription drug for oral use according to the German Commission E Monographs. Indications: Premenstrual disorders, dysmenorrhea, or climacteric [menopausal] neurovegetative ailments. Action: Estrogen-like action; luteinizing hormone suppression; binding to estrogen receptors.
8. *Spain:* No official monograph. Regulated as an OTC drug for symptomatic treatment of complaints caused by menopause, such as hot flushes, sweating, sleep-induction disturbances, tiredness, nervousness, and moodiness.
9. *Sweden:* Classified as a natural remedy intended for self-medication, requiring advanced application for marketing authorization.
10. *Switzerland:* Black Cohosh single-ingredient medicines are classified by the Interkantonale Kontrollstelle für Heilmittel (IKS-List D) as nonprescription drugs with sale limited to pharmacies and drugstores. Indications: Menopausal complaints, hot flashes, sweating, sleep disorders, nervousness, and mood disorders.
11. *United Kingdom:* Occurs in the *British Herbal Pharmacopoeia* (*BHP* 1996). Black Cohosh dried rhizome and root is an herbal medicine indicated for conditions capable of self diagnosis as specified in the General Sale List, Schedule 1 (medicinal products requiring a full product license), Table A (for internal or external use); 200-mg maximum single dose. Exemptions from licensing are contained in section 12 of the 1968 Medicines Act. Indications: Menopausal disorders, premenstrual complaints, dysmenorrhea, uterine spasm (Bradley 1992). Actions: Anti-inflammatory (*BHP* 1996), antirheumatic, endocrine (pituitary, estrogen-mimetic) activity, emmenagogue.
12. *United States:* Regulated as a dietary supplement. Black Cohosh dried rhizome and root, both whole and powdered, and Black Cohosh dry extract have been proposed for inclusion in the *United States Pharmacopeia–National Formulary.*

Ginger *Zingiber officinale* Roscoe (Fam. Zingiberaceae)

Botanical Identification—*Zingiber officinale* Roscoe. Herbaceous perennial from tuberous rhizome, aromatic due to the presence of volatile oils.

Stem: Erect, unbranched pseudostem formed by the tight overlap of sheathing leaf bases; 9 to 15 dm tall.

Leaf: Simple, alternate and two-ranked, sessile or petioles short with bases sheathing the stem and a ligule where the leaf base meets the stem; blade linear to narrowly lanceolate, 15 to 25 cm long, 1.5 to 3 cm wide; margin entire; glabrous to pubescent.

Inflorescence: Terminal spike, 3.5 to 8 cm long, 1.5 to 2 cm wide, with conspicuous spirally arranged primary bracts; usually borne on specialized leafless stems.

Flower: Perfect, bilaterally symmetric; calyx tubular with 3 lobes; corolla tube 2 to 2.5 cm long with lanceolate apical lobes, 1.5 to 2 cm long, 2 to 3.5 mm wide, greenish yellow; stamen 1, anther cream-colored with dark purple, elongated connective grasping upper part of style; staminodes 4, petaloid, 2 fused into an erect, ovate-oblong lip which is dull purple with cream mottling; ovary inferior; style 1, slender, exerted beyond connective.

Fruit: Loculicidal capsule; seeds shiny black with a white aril. Chromosome number: n = 11.

There are several different varieties and forms of *Zingiber*. The varying morphological characteristics of these are displayed in *Table 1*.

Table 1. Morphological Characteristics of Ginger from Different Areas of Production

Source	Form	Aroma	Color (External)	Oil Content
Africa	Flat surfaces, mostly peeled, starchy and fibrous; 9 cm long, 1.5 cm wide	Poor quality is recognized by its camphoraceous aroma	Uncut surface dark grayish-brown; cut surface brownish-black	1.6% (1.5% gingerol)
Australia		Citrus-like	Buff	
Bengal	Flat surfaces, scraped		Gray-brown	2% to 3% (0.6% to 1.8% gingerol)
China	Short stumpy lobes, unscraped, mostly sliced	Strong, floral to citrus	Pale brown	
Cochin	Lateral surfaces lacking cork	Strong, floral to citrus	Cream color with numerous black resin dots	1.35% to 1.5% (0.6% gingerol)
Jamaica (unbleached)	Up to 12 cm long, 1 cm wide; surfaces completely peeled; starchy and fibrous thin cortex	Delicate, citrus-like	All surfaces yellow-brown	
Japan	Up to 7 cm long, 12 mm wide; flat surfaces usually completely peeled; starchy and fibrous thick cortex	Bergamot-like	Externally gray white to light grayish-brown, often with white powder from being coated with lime	1.23%
Malabar (Cochin and Calcutta)	Cork layer completely removed, mostly treated with chalk	Citrus-like	Almost white	
Nigeria	Smaller in size than other varieties, rather less deeply scraped	Delicate	Somewhat darker than other varieties	0.7% to 1%

Historical Use—Ginger was official in the *United States Pharmacopoeia* from the first edition of 1820 through the fourteenth revision of 1950, often appearing in multiple preparations. It also appeared in all editions of the *United States Dispensatory* from 1833 through the final edition of 1973 where it was described as "a stimulant and carminative that has been used for treatment of dispepsia and flatulent colic".

Constituents—The essential oils and the pungent principles make up some of the major components of the rhizome of Ginger: 4.0% to 10.0% of the rhizome consists of an oleoresin composed of nonvolatile, pungent principles (phenols such as gingerols and their related dehydration products, shogaols); nonpungent fats and their waxes. The essential oil (1% to 3%) contains sesquiterpenes and monoterpenes, mainly geranial and nerals. Generally, but not always sesquiterpenes predominate (30% to 70%) such as zingiberene, sesquiphellandrene and beta-bisabolene, which decompose on drying and storage. The nonvolatile pungent principles include the phenylalkanones, gingerols, and the phenylalkanonols, shogaols with varying chain lengths.

Sources—*Zingiber* is cultivated in most tropical and subtropical countries to greater or lesser degrees. The world production is estimated to be 100,000 tons. China and India are reported to be the primary areas of production. Approximately 5000 tons of *Zingiber* are imported into the United States. An estimated 80% of this comes from China. In China, Sichuan and Guizhou provinces reportedly produce the largest quantities and highest quality. It is also produced in Zhejian, Shandong, Hubei, Guangdong, and Shanxi provinces. Most of the dried ginger from China available in the United States has had the cortex scraped or rubbed off before it is dried. This gives it a whitish appearance. The freshly dug root is soaked overnight in water, scraped with a knife to remove the outer cortex and then sun-dried. It has been reported that high arsenic levels in the soil of Changning County of Hunan Province, China has negatively effected *Zingiber* yields.

In India, *Zingiber* is grown on a large scale in the warm, moist regions of Madras and Cochin, and to a lesser extent in Bengal and the Punjab. Varieties grown in Bengal are reportedly the highest quality material in India. Other areas of production include Africa (Nigeria and Sierra Leone), Australia, Fiji, East Indies, Jamaica, and Hawaii. The morphological characteristics of *Zingiber* cultivated in these different areas are outlined in *Table 1*.

In older literature, Jamaican *Zingiber* is reported to be the highest quality and the most aromatic, though supplies are limited.

Collection and Cultivation—

Collection (Conservation and Ecology)—When the stems wither and are white, the rhizomes are ready for collection. Usually Ginger is harvested after 6 months of growth at the earliest, and sometimes not until as late as 20 months, or to obtain larger roots it is harvested in January or February of the second year of growth. In tropical and subtropical areas, roots are harvested as early as 4 months of growth as they tend to become fibrous and tough as they get older. As *Zingiber* matures it becomes more fibrous and stronger in flavor. Ginger harvest can be described in three stages:

1. Ginger that has been harvested early is known as green ginger and is traded as fresh ginger. It is succulent and tender, mellow, and mildly aromatic with a floral or lemony aroma and mild flavor.
2. Ginger harvested a few months later is more fibrous and drier and is collected for drying and may be sold as a full-flavored, pungent dried whole ginger.

3. The last harvest is usually around 9 months and yields the strongest ginger, which is quite dry and also richest in pungent components. This ginger is dried and then ground into powder.

Cultivation Practices—Ginger is a perennial herb that grows well at subtropical temperatures where the rainfall is at least 1.98 meters per year. The plant is sterile and is grown by vegetative means. Selected pieces of rhizome ("seed pieces" or "setts"), each bearing a bud, are planted in holes or trenches. Ideally the soil should be well-drained, rich clay loam. The growing conditions resemble those of potato cultivation. Mulching or manuring is necessary because the plant rapidly exhausts the soil of nutrients.

Ginger is susceptible to water logging and root rot. Preventive methods include using only the cleanest ginger for planting and washing it with fungicide before planting. A study growing *Zingiber* hydroponically yielded up to 125 tons per hectare in 6 to 7 months compared to 35 tons per hectare when grown in soil.

Optimal Times for Harvest: typically in December or January.

Optimal Handling and Processing Practices—After harvesting, the rhizome is cleaned and stripped of its stems and roots. Each area processes its *Zingiber* differently after harvest. This results in the different quality and commercial grades available on the market. Green *Zingiber* consists of the rhizomes sent to market without drying. Unscraped or partially scraped varieties are traded as coated or black ginger. These roots have been scalded with boiling water and dried quickly. When dry, black *Zingiber* breaks with a horny, blackish, somewhat diaphanous fracture, due to the pasty condition of the starch. White *Zingiber* is bleached usually by rubbing with chalk or lime to lighten its color and to prevent insect infestation. Preserved ginger consists of soft, yellowish-brown pieces obtained by steeping the fresh *Zingiber* in hot syrup and carefully bottling. It is soft, brown-yellow and translucent. When baked, *Zingiber* loses its pungency and acquires a bitter taste.

Drying, Storage, and Shipping—

Drying—In general, after harvest, the fresh roots are washed and the whole dark outer skin, consisting of cork and a little underlying parenchyma, is scraped away. Scraping speeds up the drying time of the crude drug. However, excessive scraping can result in lower concentrations of essential oil that is lost with the discarded epidermal tissue. After scraping, the rhizomes are then laid out on clean floors and dried in the sun for 7 to 10 days. During this time they are occasionally turned and are piled up every night. If the fresh rhizomes are too fleshy or moist, drying will take longer and the product will end up looking shriveled. To obtain a whiter product, the ginger is moistened after 5 or 6 days and dried for another 2 days at which time it is ready for export. Dried ginger is more pungent and stronger in taste than fresh ginger.

Storage—Store in a tightly closed container, protected from light and moisture, in a cool area. A study was done on Ginger harvested after 8, 9.5, 11, or 12 months. Samples were stored at 10° to 15° and 45% to 55% relative humidity or 25° to 30° and 75% relative humidity for 0, 4, or 8 weeks. Oil and oleoresin yields increased with the age of the Ginger. Room temperature storage had adverse effects but refrigerated storage for up to 4 weeks had no affect on quality. When stored for extended periods of time, ground Ginger loses its pungency.

Adulterants—Because *Zingiber* is so characteristic, unintentional adulterants are rare. However, in East Asia sometimes the much larger *Zedoary cassumer* and *Zedoary zerumbet* along with *Alpinia allughas* are used and found in

European commerce. They are easy to distinguish due to their characteristic aromas. Occasionally, Chinese sugar-candied *Zingiber* is prepared from *Alpinia galangal*.

In older literature, other herbs have reportedly been used as adulterants. These include various species of *Curcuma, Capsicum,* and Grains of Paradise *(Amomum melegueta)* added to exhausted material in order to enhance the color and pungency.

Zingiber powder is sometimes adulterated with plant starches such as those from wheat middlings, potatoes, corn, barley, rice, legumes, acorns, flaxseed meal, mannihot, oil cakes from linseed, raps, mustard, almond meal, palm kernal or olives, hazelnut shells, and mineral additives. These may be easily identified microscopically. The extent of this type of adulteration in trade is unknown.

Exhausted material should be considered an adulterant.

Global Regulatory Status—

1. *Austria:* Ginger is registered as a nonprescription drug to prevent nausea and vomiting associated with motion sickness. Official in *Austrian Pharmacopoeia.*
2. *Brazil:* Resolution n° 89/04 (simplified registration of phytotherapeuticals): Used part: roots; Used forms: extract; Administration route: oral; Nonprescription drug to prevent nausea associated with motion sickness and postsurgical nausea.
3. *Canada:* When labeled as a Traditional Herbal Medicine (THM) ginger is regulated as a nonprescription drug requiring premarket registration and assignment of a Drug Identification Number (DIN) (Health Canada, 1996).
4. *European Union:* Dried, whole or cut, rhizome of *Zingiber officinale* Roscoe, containing not less than 15 mL per kg of essential oil, calculated with reference to the anhydrous drug official in *European Pharmacopoeia* (*Ph. Eur.,* 2001).
5. *France:* Classified as a food.
6. *Germany:* The fresh or dried rhizome as well as its preparations in effective dosages are approved nonprescription drugs of the German Commission E Monographs for the treatment of dyspepsia and the prevention of motion sickness. Dried rhizome official in *German Pharmacopoeia* (*DAB,* 1999).
7. *Sweden:* Classified as food (no products marketed as natural herbal remedy, MPA, 2004)
8. *Switzerland:* Herbal medicine with positive classification (List D), sale limited to pharmacies and drugstores without prescription. Ginger is indicated to prevent motion sickness and for the treatment of dispeptic complaints. Dried rhizome official in *Swiss Pharmacopoeia*.
9. *United Kingdom:* Included in the General Sale List (GSL) of the Medicines and Healthcare Products Regulatory Agency (MHRA). Dried rhizome official in *British Pharmacopoeia* (*BP,* 1980).
10. *United States:* Generally Recognized as Safe (GRAS) (U.S. FDA, 1998). Dietary supplement (*USC,* 1994). Dried rhizome, powdered dried rhizome and ginger tincture official in the *U.S. Pharmacopeia* (*USP 28;* 2005, 2091–2093).

Valerian *Valeriana officinalis* L. (Fam. Valerianaceae)

Botanical Identification—*Valeriana officinalis* L. Herbacious perennial, rhizomatous.

Stem: Solitary, hollow, 15 to 150 cm.

Leaf: Basal and cauline, opposite, oddly once pinnately lobed, lobes 11 to 21 lanceolate, entire or dentate, basal leaves petiolate, cauline leaves subsessile to clasping.

Inflorescence: Compound cyme, terminal or axillary, many pale pink to white, strongly scented flowers.

Flower: Calyx 5-lobed, lobes inconspicuous in flower, becoming elongate and pappus-like in fruit, corolla funnelform, slightly saccate at the base, 5-lobed, tube 4 mm, lobes 1 mm, stamens 3, filaments attached to corolla tube alternate to corolla lobes, ovary inferior, tri-loculate, uni-ovulate, only 1 locule fertile, stigma tripartite.

Fruit: Achene crowned by persistent calyx, lanceolate-oblong, 4.5 to 5 mm, hairy or glabrous. Populations of *V. officinalis* range in ploidy level from diploid to tetraploid or octaploid. British *V. officinalis* is usually octaploid, and central European supplies are tetraploid.

There are three subspecies of *V. officinalis*: ssp. *officinalis*, ssp. *collina* (Wallr.) Nyman, and ssp. *sambucifolia* (Mikan fil.) Celak. All three of these subspecies, as well as the other European species of valerian, *V. repens* Host, have been considered acceptable source material for medicinal preparations.

Macroscopic Identification—Various chemotypes will have slightly different characteristics. When dried, the whole rhizome is up to 50 mm long and up to 30 mm in diameter, obconical to cylindrical, with an elongated or compressed base. It has a yellowish-brown to dark brown exterior with a circular stem and leaf scars. The rhizome contains numerous thick, light to dark brown rootlets that are located around a thin ligneous cord. The root is longitudinally wrinkled and approximately 100 mm long and 1 to 3 mm in diameter, almost cylindrical and almost the same color as the rhizome. In longitudinal section, the pith exhibits a central cavity transversed by septa. The stolons are 20 to 50 mm long, pale yellowish grey with prominent nodes separated by longitudinally striated internodes. It is commonly sliced in half for ease of cleaning. The rootlets, which contain the majority of the essential oil, are brittle and break in short, horny fractures and are whitish or yellowish internally. Aroma: When dried properly, *V. officinalis* L., s.l. has only a very faint characteristic, valeric acid-like aroma that becomes stronger as it ages. Improperly dried or old material possesses a strong and characteristic odor due to the enzymatic hydrolysis of esters of the valepotriates (isovaleric acid and hydroxyvaleric acid). Taste: Mildly sweet and camphoraceous with a slightly bitter and spicy aftertaste.

Historical Use—Valerian was official in the *United States Pharmacopeia* from the first edition of 1820 through the eleventh revison of 1930, often appearing in multiple preparations. At its peak from 1850 through 1880 it appeared six to seven times in different preparations. Valerian is among the top 30 most listed botanicals in the history of the *USP*. The root of Valerian has been used as a sedative and spasmolytic in Europe since the 16th century.

Constituents—Major constituents of Valerian have been identified as sesquiterpenes of volatile oils and iridoids (epoxy-triesters) known as valepotriates. The total content of volatile oil varies widely within a single species and between different species. European *Valeriana officinalis* L. usually contains 0.1% to 2.8% volatile oil. The oil consists of mixtures of monoterpene and sesquiterpene derivatives. The amount of valepotriates present also varies widely between species and genera and even within a species, generally ranging from 0.5% to 1.2%. Valepotriates are particularly unstable; they decompose easily under the effect of moisture, temperatures above 40° (104°F), or acidity (pH <3).

Valerian also contains small amounts of aliphatic acids, alkaloids, amino acids, phenolic acids, flavonoids, free fatty acids, sugars, and salts. Valerian constituents that have possible sedative effects include acetoxyvalerenic acid, 1-acevaltrate, baldrinal, didrovaltrate, hydroxyvalerenic acid, kessane derivatives, valeranone, valerenal, valerenic acid, and valtrate.

Sources—Valerian is found in damp or dry meadows, scrub, or woods in most of Europe, but rare in the south, and is cultivated and naturalized in North America. Valerian is cultivated in Britain, Belgium, Eastern Europe, France, Germany, Holland, Japan, the Netherlands, North America, and Russia. The majority of standardized extract products and crude cut and sifted material on the domestic market are prepared from European supplies. A large number of liquid extracts are prepared from domestically cultivated material. Many species other than *V. officinalis* are reported to be traded as medicinal valerian. These include *V. edulis* Nutt. ex Torr. & A. Gray, *V. corneana* Briq. k, *V. stubendorfi* Kreyer ex Kom., *V. amurensis* P. Smirn. ex Kom., *V. hardwickii* Wall., *V. exaltata* Mikan, and *V. wallichi* DC. syn. *V. jatamansi* Jones.* The most frequently used North American species include *V. sitchensis* Bong and *V. edulis* Nutt.* = *V. edulis* Nutt. ex Torr. & Gray ssp. *procera.* Other species reported to be used locally include *V. arizonica* Gray, *V. capitata* Pall ex Link., *V. diocia* L., and *V. scouleri* Rydb. Detailed chemical analyses of most American species are lacking. A limited number of assays of material cultivated in the Pacific Northwest show varying levels of essential oil ranging from 0.4% to 1.3%. Valerenic acid and valepotriates have been found to be present in fresh and dry samples of *V. sitchensis* Bong. *V. sitchensis* Bong exhibits a strong pungency when fresh. High quality material is reported to contain from 1.0% to 1.5% essential oil, ≥30% extractable matter, and ≥0.5% valerenic acid.

Collection and Cultivation—

Collection (Conservation and Ecology)—The majority of Valerian in trade comes from cultivated material. Harvest times will vary geographically. The composition of the essential oil varies greatly among different populations of the same subspecies and even between the same population of plants from year to year. Essential oil content also varies with genotypes, harvest times, growing conditions, age of root, drying techniques, and method of analysis. It has been reported that valerian harvested in higher elevations, grown in dryer regions, or cultivated in phosphate-rich soil yields relatively high levels of essential oil.

Older literature reports that valerian should be harvested in the fall, between August and September, preferably in the second year of growth. Analyses of material cultivated in the Netherlands report that the majority of constituents, including the essential oil and valerenic acid, were highest in roots harvested in the first year of growth with essential oil being highest in September and November (1.2% to 2.1%). The next highest level of essential oil was reported for material harvested in March (0.9% to 1.6%). Valerenic acid and its derivatives were found to be highest in February and March (0.7% to 0.9%) followed by material harvested in September (0.5% to 0.7%) and then in January (0.3% to 0.4%). From a commercial standpoint, it is more cost effective to harvest the roots in the same year the plants are sown than in the second year.

Cultivation Practices—Sowing seeds has been reported to be preferred over planting of seedlings. Best results were achieved by flat field planting at row spacings of 50 cm and a seed rate of 3 kg per hectare. Cutting off the flowering tops before the plant has set seed causes the rhizome to develop more fully.

Optimal Times for Harvest—Wagner reports that harvest should take place in the morning during relatively cool weather, a general recommendation for roots rich in essential oils.

Optimal Handling and Processing Practices—The essential oil is located in the hypodermis of the rhizome in large thin-walled cells. Therefore, care must be taken not to damage these cells during handling. Excess washing of the roots

* V. wallichi DC. and V. edulis Nutt. reportedly are lacking in valerenic acid and its derivatives.

In-Process Revision

can result in a significant reduction of extractive matter. Because of the sensitivity of volatile oils to heat, it is necessary to minimize the amount of time generated in the grinding or powdering process by doing small lots at a time, with frequent interruptions in run times, or by utilizing a cryogenic grinder.

Drying, Storage, and Shipping—

Drying—For maximum preservation of the essential oils, Valerian should be dried at 40° with a flow rate of 0.05 kg per sec per m^2. Alternatively, drying at 20° for approximately 10 days, shade drying at approximately 45°, low temperature vacuum-drying, and freeze-drying are also reported to be appropriate drying techniques.

Careless or prolonged drying produces a darker color in the roots and results in the hydrolysis of the isovalerianic esters and the liberation of isovaleric and hydroxyisovaleric acid. This produces the characteristic valerianic aroma. Properly dried Valerian will produce this same aroma over time.

Storage—Store in closed containers protected from light, air, and moisture. Hydroxyvalerenic acid, a decomposition product of acetoxyvalerenic acid, is formed when the herb is stored at too high humidity.

Improper storage conditions can cause significant deterioration of the material. Although the essential oil is relatively stable, it can evaporate with excessive exposure to air. The essential oil can degrade quickly in powdered material. In powdered root, the essential oil content can decrease by 50% within 6 months.

Valepotriates are sensitive to humidity, temperatures above 40°, and acid media (pH <3) and are generally not detected in commercial products after 60 days.

Adulterants—Other species of Valerian: An unidentified *Apiaceae* species may be found in valerian trade. Adulteration of Valerian in the American market is not common. Many species other than *V. officinalis* are reported to be traded as medicinal Valerian. These include *V. edulis* Nutt. ex Torr. & A. Gray, *V. coreana* Briq.k, *V. stubendorfi* Kreyer ex Kom., *V. amurensis* P. Smirn. ex Kom., *V. hardwickii* Wall, *V. exaltata* Mikan, and *V. wallichi* DC. syn. *V. jatamansi* Jones.

Global Regulatory Status—

1. *Austria:* Official in *Austrian Pharmacopoeia.*
2. *Belguim:* Oral use as Traditional Herbal Medicine (THM), accepted for specific indications.
3. *Canada:* Dried root in tablet, capsule, powder, extract, tincture, or tea bags labeled as THM indicated as sleep aid or sedative; requires premarket authorization and assignment of a Drug Identification Number (DIN) and conformance with the Valerian Labeling Standard.
4. *European Union:* "Whole", dried, underground parts containing no less than (NLT) 0.5% volatile oil, and "cut", dried, underground parts (NLT 0.3% volatile oil; NLT 0.17% sesquiterpenic acids), official in *European Pharmacopoeia* (*Ph. Eur.,* 2001).
5. *France:* Oral use as THM accepted for specified indications. Dried root (NLT 0.5% volatile oil), official in *French Pharmacopoeia.*
6. *Germany:* Dried root, for preparation of tea infusion, tincture, or extract is an approved nonprescription drug of the German Commission E Monographs. Tea infusion and hydro-alcoholic tincture forms are approved nonprescription drugs of the German Standard License monographs. Extract or volatile oil for balneotherapy (bath therapy) is approved in the German Commission B8 Monographs. Dry native extract, 3~6 : 1 (w/w), is official in *German Pharmacopoeia* (*DAB,* 1999). The mother tincture (and liquid dilutions) of dried root are official preparations of the *German Homeopathic Pharmacopoeia* (*GHP,* 1993).

7. *Italy:* Dried root (NLT 0.5% volatile oil) official in *Italian Pharmacopoeia* (*Ph. Ital.* 1991).
8. *Russian Federation:* Official in *State Pharmacopoeia of the Union of Soviet Socialist Republics*.
9. *Sweden:* Classified as Natural Remedy for self-medication requiring advance application for marketing authorization. A valerian monograph is published in the Medical Products Agency (MPA) "Authorised Natural Remedies", which lists four registered monopreparations and 10 multiple-herb (with passionflower, lemon balm, or hops) preparations (MPA, 1997 and 2001; Tunón, 1999). Two valerian products (Baldrian-Dispert and Neurol) are regulated as Pharmaceutical Specialties, or conventional OTC drugs.
10. *Switzerland:* Herbal medicine with positive classification (List D) by the Interkantonale Konstrollstelle für Heilmittel (IKS) and corresponding sales category D with sale limited to pharmacies and drugstores, without prescription. There are 62 valerian phytomedicines and 11 homeopathic preparations listed in the Swiss Codex 2000/01. Dried root official in *Swiss Pharmacopoeia* 1997.
11. *United Kingdom:* General Sale List (GSL), Schedule 1, Table A. Dried root (NLT 0.5% volatile oil) and powdered dried root (NLT 0.3% volatile oil) official in *British Pharmacopoeia.*
12. *United States:* Generally Recognized as Safe (GRAS) (U.S. FDA, 1998). Dietary supplement (USC, 1994). Application for OTC approval for use as a nighttime sleep aid is pending. Valerian root (NLT 0.5% volatile oil; NLT 0.05% valerenic acid) and powdered valerian (NLT 0.3% volatile oil; NLT 0.04% valerenic acid) are official in *U.S. Pharmacopeia* (*USP 28;*2005, 2133–2135). Powdered Valerian extract, 4~7 : 1 (w/w) (NLT 0.3% valerenic acid) added to *NF 19, 1st Supplement* (*USP,* 2000). The mother tincture 1 : 10 (w/v), 55% alcohol (v/v), of fresh or dried root, is an OTC Class C drug official in *Homeopathic Pharmacopoeia of the United States* (*HPUS,* 1993).▲*USP29*

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Acetanilide, *USP 28* page 2795. For safety reasons, it is proposed to eliminate all references to smell and taste in the specifications for this and the following reagents.

Acetyl Chloride
Acetylcholine Chloride
4-Amino-6-chloro-1,3-benzenedisulfonamide
Amyl Acetate
tert-Amyl Alcohol
L-Asparagine
Benzaldehyde
Benzphetamine Hydrochloride
Benzyltrimethylammonium Chloride
Biphenyl
N-Bromosuccinimide
2,3-Butanedione
n-Butyl Chloride
Cadmium Acetate
Calcium Citrate
Calcium Lactate
Casein
Charcoal, Activated
Chlorobenzene
Congo Red
Cyclohexanol
o-Dichlorobenzene
Dicyclohexylamine
Diidofluorescein
1,2-Dimethoxyethane
Ethyl Cyanoacetate
Ethylene Glycol
Ferric Ammonium Citrate
Guaiacol
n-Heptane, Chromatographic
Hexamethyldisilazane
Hexane, Solvent
Inositol
Isopropylamine
Maleic Acid

In-Process Revision

Methyl Acetate
1-Naphthol
2-Naphthol
5-Nitro-1,10-phenanthroline
Nonylphenoxypoly(ethyleneoxy)ethanol
Para-aminobenzoic Acid
Paraformaldehyde
Propionic Anhydride
Pyrrole
Rose Bengal Sodium
Silver Oxide
Sodium Arsenite
Sodium Chromate
Sodium Glycocholate
Tetramethylammonium Hydroxide
Thioglycolic Acid
Thymol
n-Tricosane
Triethylamine

(HDQ: M. Marques) RTS—42098-1

Change to read:

Acetanilide, C_8H_9NO—**135.16**—White, shiny crystals, usually in scales, or a white, crystalline powder. ~~Is odorless and~~

▲▲*USP29*
Is stable in air. Freely soluble in alcohol and in chloroform; soluble in boiling water, in ether, and in glycerin; slightly soluble in water.

Melting range ⟨741⟩: between 114° and 116°.

Reaction—Its saturated solution is neutral to litmus.

Loss on drying ⟨731⟩—Dry it over sulfuric acid for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition (Reagent test): not more than 0.05%.

BRIEFING

Acetyl Chloride, *USP 28* page 2795—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-2

Change to read:

Acetyl Chloride, CH_3COCl—**78.50**—Clear, colorless liquid. ~~having a strong, pungent odor.~~

▲▲*USP29*
Is decomposed by water and by alcohol. Miscible with benzene and with chloroform. Use ACS reagent grade.

Specific gravity ⟨841⟩: about 1.1.

BRIEFING

Acetylcholine Chloride, *USP 28* page 2795—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-3

Change to read:

Acetylcholine Chloride, $[CH_3COOCH_2CH_2N(CH_3)_3]Cl$—**181.66**—White, crystalline ~~odorless or nearly odorless~~

▲▲*USP29*
powder. Very deliquescent; very soluble in water; freely soluble in alcohol.

Melting range ⟨741⟩—When previously dried at 110° in a capillary tube for 1 hour, it melts between 149° and 152°.

Reaction—Its 1 in 10 solution is neutral to litmus.

Residue on ignition (Reagent test): negligible, from 200 mg.

Solubility in alcohol—A solution of 500 mg in 5 mL of alcohol is complete and colorless.

Percent of acetyl (CH_3CO)—Weigh accurately about 400 mg, previously dried at 105° for 3 hours, and dissolve in 15 mL of water in a glass-stoppered conical flask. Add 40.0 mL of 0.1 N sodium hydroxide VS, and heat on a steam bath for 30 minutes. Insert the stopper, allow to cool, add phenolphthalein TS, and titrate the excess alkali with 0.1 N sulfuric acid VS. Determine the exact normality of the 0.1 N sodium hydroxide by titrating 40.0 mL after it has been treated in the same manner as in the test. Each mL of 0.1 N sodium hydroxide is equivalent to 4.305 mg of CH_3CO. Between 23.2% and 24.2% is found.

Percent of chlorine (Cl)—Weigh accurately about 400 mg, previously dried at 105° for 3 hours, and dissolve in 50 mL of water in a glass-stoppered, 125-mL flask. Add with agitation 30.0 mL of 0.1 N silver nitrate VS, then add 5 mL of nitric acid and 5 mL of nitrobenzene, shake, 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 is equivalent to 3.545 mg of Cl. Between 19.3% and 19.8% of Cl is found.

BRIEFING

4-Amino-6-chloro-1,3-benzenedisulfonamide, *USP 28* page 2797—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-4

Change to read:

4-Amino-6-chloro-1,3-benzenedisulfonamide, $C_6H_8ClN_3O_4S_2$—**285.73**—White ~~odorless~~

▲▲*USP29*
powder. Insoluble in water and in chloroform; soluble in ammonia TS.

Residue on ignition (Reagent test): not more than 2 mg from 2 g (0.1%).

Absorbance—A 1 in 200,000 solution in methanol exhibits absorbance maxima at about 223 nm, 265 nm, and 312 nm. Its absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩) at 265 nm is about 64.0.

BRIEFING

Amyl Acetate, *USP 28* page 2799—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42048-5

Change to read:

Amyl Acetate (*Isoamyl Acetate*), $CH_3CO_2C_5H_{11}$—**130.18**—Clear, colorless liquid. ~~with a characteristic, banana oil–like odor.~~

▲▲*USP29*
Slightly soluble in water. Miscible with alcohol, with amyl alcohol, with benzene, and with ether.

Specific gravity ⟨841⟩: about 0.87.

Boiling range (Reagent test, *Method I*): not less than 90%, between 137° and 142°.

Solubility in diluted alcohol—A 1.0-mL portion dissolves in 20 mL of diluted alcohol to form a clear solution.

Acidity—Add 5.0 mL to 40 mL of neutralized alcohol, and, if the pink color is discharged, titrate with 0.10 N sodium hydroxide: not more than 0.20 mL is required to restore the pink color (about 0.02% as CH_3COOH).

Water—A 5-mL portion gives a clear solution with 5 mL of carbon disulfide.

BRIEFING

***tert*-Amyl Alcohol,** *USP 28* page 2799—See briefing under *Acetanilide*.

(HDQ: M. Marques) RTS—42098-6

Change to read:

***tert*-Amyl Alcohol,** $C_5H_{12}O$—**88.15**—Clear, colorless, flammable, volatile liquid. ~~with a characteristic odor.~~

▲▲*USP29*
Specific gravity ⟨841⟩: about 0.81.

Boiling range (Reagent test): not less than 95%, between 100° and 103°.

Residue on evaporation—Evaporate 50 mL (40 g) on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1.6 mg (0.004%).

Acids and *esters*—Dilute 20 mL with 20 mL of alcohol, add 5.0 mL of 0.1 N sodium hydroxide VS, and reflux gently for 10 minutes. Cool, add 2 drops of phenolphthalein TS, and titrate the excess sodium hydroxide with 0.1 N hydrochloric acid VS: not more than 0.75 mL of the 0.10 N sodium hydroxide is consumed, correction being made for the amount consumed in a blank (0.06% as amyl acetate).

Aldehydes—Shake 5 mL with 5 mL of potassium hydroxide solution (30 in 100) in a glass-stoppered cylinder for 5 minutes, and allow to separate: no color develops in either layer.

BRIEFING

L-Asparagine, *USP 28* page 2801—See briefing under *Acetanilide*.

(HDQ: M. Marques) RTS—42098-7

Change to read:

L-Asparagine (L-*2-Aminosuccinamic Acid*), $COOHCH(NH_2)CH_2CONH_2 \cdot H_2O$—**150.13**—Colorless ~~odorless~~

▲▲*USP29*
crystals. One g dissolves in 50 mL of water; soluble in acids and in alkalies; insoluble in alcohol and in ether. Its neutral or alkaline solutions are levorotatory; its acid solutions are dextrorotatory.

Specific rotation ⟨781⟩: between +31° and +33°, determined in a solution in diluted hydrochloric acid containing the equivalent of 5 g (on the anhydrous basis, as determined by drying at 105° for 5 hours) in each 100 mL.

Residue on ignition (Reagent test): not more than 0.1%.

Chloride (Reagent test)—One g shows not more than 0.03 mg of Cl (0.003%).

Sulfate (Reagent test, *Method I*)—One g shows not more than 0.05 mg of SO_4 (0.005%).

Heavy metals (Reagent test): 0.002%.

Nitrogen content, *Method II* ⟨461⟩: between 18.4% and 18.8% of N is found.

BRIEFING

Benzaldehyde, *USP 28* page 2801—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-8

Change to read:

Benzaldehyde, C_7H_6O—**106.12**—Colorless, strongly refractive liquid. ~~having an odor resembling that of bitter almond oil.~~

▲▲*USP29*
Soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils.

In-Process Revision

Assay—Pipet about 1 mL into a tared, glass-stoppered weighing bottle, and weigh accurately. Loosen the stopper, and transfer both the weighing bottle and its contents to a 250-mL conical flask containing 25 mL of a hydro-alcoholic solution of hydroxylamine hydrochloride (prepared by dissolving 34.7 g of hydroxylamine hydrochloride in 160 mL of water, then adding alcohol to make 1000 mL, and neutralizing to bromophenol blue by the addition of sodium hydroxide TS). Using a graduated cylinder to measure the volume, rinse the sides of the flask with an additional 50 mL of this reagent solution. Allow the solution to stand for 10 minutes, add 1 mL of bromophenol blue TS, and titrate the liberated hydrochloric acid with 1 N sodium hydroxide VS. Perform a blank determination with the same quantities of the same reagents, and make any necessary correction. Each mL of 1 N sodium hydroxide consumed is equivalent to 106.1 mg of C_7H_6O. Not less than 98% is found.

Specific gravity ⟨841⟩: between 1.041 and 1.046.

Refractive index ⟨831⟩: between 1.5440 and 1.5465 at 20°.

Hydrocyanic acid—Shake 0.5 mL with 5 mL of water, add 0.5 mL of sodium hydroxide TS and 0.1 mL of ferrous sulfate TS, and warm the mixture gently. Add a slight excess of hydrochloric acid: no greenish-blue color or blue precipitate is observed within 15 minutes.

BRIEFING

Benzphetamine Hydrochloride, *USP 28* page 2802—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-9

Change to read:

Benzphetamine Hydrochloride, $C_{17}H_{21}N \cdot HCl$—**275.82**—White to off-white, ~~odorless,~~

▲▲*USP29*
crystalline powder. Freely soluble in water, in alcohol, and in chloroform; slightly soluble in ether.

Assay—Dissolve about 500 mg, accurately weighed, in a mixture of 50 mL of glacial acetic acid and 10 mL of mercuric acetate TS, add 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 27.58 mg of $C_{17}H_{21}N \cdot HCl$. Between 98.0% and 101.0%, calculated on the dried basis, is found.

Melting range ⟨741⟩: between 152° and 158°.

Specific rotation ⟨781⟩: between +22° and +26°, determined in a solution containing 200 mg in 10 mL, the specimen having been previously dried in vacuum at 60° for 3 hours.

Loss on drying ⟨731⟩—Dry in vacuum at 60° for 3 hours: it loses not more than 1% of its weight.

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

BRIEFING

Benzyltrimethylammonium Chloride, *USP 28* page 2802—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-10

Change to read:

Benzyltrimethylammonium Chloride, $C_6H_5CH_2N(CH_3)_3Cl$—**185.69**—Available as a 60% aqueous solution. Is clear and is colorless or not more than slightly yellow. ~~, and has a slight amine-like odor.~~

▲▲*USP29*
Assay—Pipet 2 mL into a 50-mL volumetric flask, and add water to volume. Pipet 20 mL of the solution into a 125-mL conical flask, add about 30 mL of water, then add 0.25 mL of dichlorofluorescein TS, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 18.57 mg of $C_6H_5CH_2N(CH_3)_3Cl$. Between 59.5% and 60.5% is found.

BRIEFING

Biphenyl, *USP 28* page 2803—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-11

Change to read:

Biphenyl, $C_{12}H_{10}$—**154.21**—Colorless to white crystals or crystalline powder. ~~, having a pleasant odor.~~

▲▲*USP29*
Insoluble in water; soluble in alcohol and in ether. Boils at about 254°.

Melting range ⟨741⟩: between 68° and 72°.

BRIEFING

***N*-Bromosuccinimide,** *USP 28* page 2804—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-12

Change to read:

***N*-Bromosuccinimide,** $C_4H_4BrNO_2$—**177.98**—White to off-white crystals or powder. ~~, having a faint odor.~~

▲▲*USP29*

Freely soluble in water, acetone, and glacial acetic acid. *[Caution—Highly irritating to eyes, skin, and mucous membranes.]*

Assay—Transfer 200 mg, accurately weighed, to a conical flask, add 25 mL of 0.5 N alcoholic potassium hydroxide, cover with a watch glass, heat to boiling, and boil for 5 minutes. Cool, transfer the solution to a beaker, rinsing the flask with water until the total volume of solution plus rinsings is about 100 mL, and add 10 mL of glacial acetic acid. Insert suitable electrodes, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Each mL of 0.1 N silver nitrate is equivalent to 17.80 mg of $C_4H_4BrNO_2$. Not less than 98% is found.

BRIEFING

2,3-Butanedione, *USP 28* page 2804—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-13

Change to read:

2,3-Butanedione (*Diacetyl*), $CH_3COCOCH_3$—**86.09**—Bright yellow to yellowish-green liquid. ~~having a strong, pungent odor.~~

▲▲*USP29*
Soluble in water. Miscible with alcohol and with ether. Boils at about 88°.

Assay—

HYDROXYLAMINE HYDROCHLORIDE SOLUTION—Dissolve 20 g of hydroxylamine hydrochloride in 40 mL of water, and dilute with alcohol to 400 mL. Add, with stirring, 300 mL of 0.5 N alcoholic potassium hydroxide, and filter. Discard after 2 days.

PROCEDURE—Transfer about 1 g, accurately weighed, to a glass-stoppered, 250-mL flask, add 75.0 mL of *Hydroxylamine hydrochloride solution,* and insert the stopper in the flask. Reflux the mixture for 1 hour, then cool to room temperature. Add bromophenol blue TS, and titrate with 0.5 N hydrochloric acid VS to a greenish-yellow endpoint. [NOTE—Alternatively, the solution may be titrated potentiometrically to a pH of 3.4.] Perform a blank test with the same quantities of reagent used for the test specimen, and make any necessary correction. Each mL of 0.5 N hydrochloric acid is equivalent to 43.05 mg of $CH_3COCOCH_3$. Not less than 97% of $CH_3COCOCH_3$ is found.

Congealing temperature ⟨651⟩: between –2.0° and –5.5°.

Refractive index ⟨831⟩: between 1.3935 and 1.3965, at 20°.

Specific gravity ⟨841⟩: about 0.98.

BRIEFING

***n*-Butyl Chloride,** *USP 28* page 2805—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-16

Change to read:

***n*-Butyl Chloride** (*1-Chlorobutane*), C_4H_9Cl—**92.57**—Clear, colorless, volatile liquid. ~~having a slight, characteristic odor.~~

▲▲*USP29*
Highly flammable. Practically insoluble in water. Miscible with alcohol and with ether.

Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying the article: a 3-mm × 1.8-m stainless steel column packed with phase G16 on support S1. Helium, flowing at a rate of about 40 mL per minute, is the carrier gas, the detector temperature is about 310°, the injection port temperature is about 230°, and the column temperature is programmed to rise at 10° per minute from 35° to 150°. A flame-ionization detector is employed.

Boiling range ⟨721⟩: between 76° and 80°, within a 2° range.

Refractive index ⟨831⟩: between 1.4015 and 1.4035 at 20°.

Acidity—Add phenolphthalein TS to 75 mL, and titrate with 0.1 N potassium hydroxide in methanol to a faint pink color that persists, with shaking, for 1.5 seconds: not more than 0.91 mL is required (about 0.005% as HCl).

Water ⟨921⟩: not more than 0.02%, determined by the *Titrimetric Method*.

Residue after evaporation—Evaporate about 60 mL (50 g), accurately weighed, in a tared platinum dish on a steam bath, and dry at 105° for 1 hour: not more than 0.005% is found.

BRIEFING

Cadmium Acetate, *USP 28* page 2805—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-17

Change to read:

Cadmium Acetate, $C_4H_6CdO_4 \cdot 2H_2O$—**266.53**—Colorless, transparent to translucent crystals. ~~Is odorless or has a slight odor of acetic acid.~~

▲▲*USP29*
Freely soluble in water; soluble in alcohol.

Insoluble matter (Reagent test): not more than 1 mg, from 20 g (0.005%).

Chloride (Reagent test)—One g shows not more than 0.01 mg of Cl (0.001%).

In-Process Revision

Sulfate (Reagent test, *Method II*)—Dissolve 10 g in 100 mL of water, add 1 mL of hydrochloric acid, and filter: the residue weighs not more than 1.2 mg more than the residue obtained in a complete blank test (0.005%).

Substances not precipitated by hydrogen sulfide—Dissolve 2 g in a mixture of 135 mL of water and 15 mL of 1 N sulfuric acid, heat to boiling, and pass a rapid stream of hydrogen sulfide through the solution as it cools. Filter, and to 75 mL of the clear filtrate add 0.25 mL of sulfuric acid, then evaporate to dryness, and ignite gently: the residue weighs not more than 1 mg (0.1%).

BRIEFING

Calcium Citrate, *USP 28* page 2806—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-18

Change to read:

Calcium Citrate, $Ca_3(C_6H_5O_7)_2 \cdot 4H_2O$—**570.49**—A white, ~~odorless,~~

▲▲*USP29*
crystalline powder. Slightly soluble in water; freely soluble in 3 N hydrochloric acid and in 2 N nitric acid; insoluble in alcohol. To 15 mL of hot 2 N sulfuric acid add in small portions and with stirring about 500 mg of calcium citrate. Boil the mixture for 5 minutes, and filter while hot: the cooled filtrate responds to the identification test for *Citrate* ⟨191⟩.

Assay—Accurately weigh about 400 mg of the salt, previously dried at 150° to constant weight, and transfer to a 250-mL beaker. Dissolve the test specimen in 150 mL of water containing 2 mL of 3 N hydrochloric acid, add 15 mL of 1 N sodium hydroxide and 250 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution turns deep blue in color. Each mL of 0.05 M edetate disodium is equivalent to 8.307 mg of $Ca_3(C_6H_5O_7)_2$: between 97.5% and 101% is found.

Calcium oxide and carbonate—Triturate 1 g of calcium citrate with 5 mL of water for 1 minute: the mixture does not turn red litmus blue. Then add 5 mL of warm 3 N hydrochloric acid: only a few isolated bubbles escape.

Hydrochloric acid-insoluble matter—Dissolve 5 g by heating with a mixture of 10 mL of hydrochloric acid and 50 mL of water for 30 minutes: not more than 2.5 mg of insoluble residue remains (0.05%).

Loss on drying ⟨731⟩—Dry it at 150° to constant weight: it loses between 12.2% and 13.3% of its weight.

Arsenic ⟨211⟩—Proceed with 0.50 g as directed for organic compounds (6 ppm of As).

Heavy metals, Method I ⟨231⟩: 0.002%.

BRIEFING

Calcium Lactate, *USP 28* page 2806—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-19

Change to read:

Calcium Lactate, $(CH_3CHOHCOO)_2Ca \cdot 5H_2O$—**308.29**—White~~, almost odorless~~

▲▲*USP29*
granules or powder. Is somewhat efflorescent and at 120° becomes anhydrous. One g dissolves in 20 mL of water; practically insoluble in alcohol. Store it in tight containers.

Assay—Accurately weigh about 500 mg, previously dried at 120° for 4 hours, transfer to a suitable container, and dissolve in 150 mL of water containing 2 mL of diluted hydrochloric acid. Add 15 mL of sodium hydroxide TS and 300 mg of hydroxy naphthol blue indicator, 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 10.91 mg of $C_6H_{10}CaO_6$. Not less than 98% is found.

Loss on drying ⟨731⟩—Dry it at 120° for 4 hours: it loses between 25.0% and 30.0% of its weight.

Acidity—Add phenolphthalein TS to 20 mL of a 1 in 20 solution, and titrate with 0.10 N sodium hydroxide: not more than 0.50 mL is required to produce a pink color.

Heavy metals (Reagent test)—Dissolve 1 g in 2.5 mL of diluted hydrochloric 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 0.02 mg of added Pb (0.002%).

Magnesium and *alkali salts*—Mix 1 g with 40 mL of water, carefully add 5 mL of hydrochloric acid, heat the solution, boil for 1 minute, and add rapidly 40 mL of oxalic acid TS. Add immediately to the warm mixture 2 drops of methyl red TS, then add ammonia TS dropwise, from a buret, until the mixture is just alkaline. Cool to room temperature, transfer to a 100-mL graduated cylinder, dilute with water to 100 mL, mix, and allow to stand for 4 hours or overnight. Filter, and transfer to a platinum dish 50 mL of the clear filtrate, to which has been added 0.5 mL of sulfuric acid. Evaporate the mixture on a steam bath to a small bulk. Carefully heat over a free flame to dryness, and continue heating to complete decomposition and volatilization of ammonium salts. Finally ignite the residue at 800 ± 25° for 15 minutes: the residue weighs not more than 5 mg (1%).

Volatile fatty acid—Stir about 500 mg with 1 mL of sulfuric acid, and warm: the mixture does not emit an odor of volatile fatty acid.

BRIEFING

Casein, *USP 28* page 2807—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-20

Change to read:

Casein—White or slightly yellow, ~~odorless,~~

▲▲*USP29*
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 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

Charcoal, Activated, *USP 28* page 2808—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-21

Change to read:

Charcoal, Activated (*Activated Carbon; Decolorizing Carbon*)—A fine, black~~, odorless~~

▲▲*USP29*
powder, which is the residue from the destructive distillation of various organic materials, treated to increase its high capacity for adsorbing organic coloring substances, as well as nitrogenous bases.

Adsorptive power—Dissolve 100 mg of strychnine sulfate in 50 mL of water, add 1 g of the test specimen, shake during 5 minutes, and filter through a dry filter, rejecting the first 10 mL of the filtrate. To a 10-mL portion of the subsequent filtrate add 1 drop of hydrochloric acid and 5 drops of mercuric iodide TS: no turbidity is produced.

Residue on ignition (Reagent test)—Ignite 500 mg: the residue weighs not more than 20 mg (4.0%).

Reaction—Boil 2 g with 50 mL of water for 5 minutes, allow to cool, restore the original volume by the addition of sufficient water, and filter: the filtrate is colorless and is neutral to litmus paper.

Acid-soluble substances—Boil 1.0 g with 25 mL of dilute hydrochloric acid (1 in 5) for 5 minutes, filter into a tared porcelain crucible, and wash the residue with 10 mL of hot water, adding the washings to the filtrate. To the combined filtrate and washings add 1 mL of sulfuric acid, evaporate to dryness, and ignite to constant weight: the residue weighs not more than 35 mg (3.5%).

Alcohol-soluble substances—Boil 2 g with 40 mL of alcohol for 5 minutes under a reflux condenser, and filter. Evaporate 20 mL of the filtrate on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 2 mg (0.2%).

Uncarbonized constituents—To 250 mg add 10 mL of sodium hydroxide TS, heat to boiling, and filter: the filtrate is colorless.

Chloride (Reagent test)—A 5-mL portion of the filtrate obtained in the test for *Reaction* shows not more than 0.04 mg of Cl (0.02%).

Sulfate (Reagent test, *Method I*)—A 5-mL portion of the filtrate from the test for *Reaction* shows not more than 0.3 mg of SO_4 (0.15%).

Sulfide—Place 1 g in a small flask with a narrow neck, add 35 mL of water and 5 mL of hydrochloric acid, and boil gently: the escaping vapors do not darken paper moistened with lead acetate TS.

BRIEFING

Chlorobenzene, *USP 28* page 2809—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-23

Change to read:

Chlorobenzene, C_6H_5Cl—**112.56**—Clear, colorless liquid. ~~having a characteristic odor.~~

▲▲*USP29*
Insoluble in water; soluble in alcohol, in benzene, in chloroform, and in ether. Use ACS reagent grade.

BRIEFING

Congo Red, *USP 28* page 2810—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-25

Change to read:

Congo Red, $C_{32}H_{22}N_6Na_2O_6S_2$—**696.67**—A dark red or reddish-brown powder. ~~Is odorless and~~

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▲▲*USP29*
Decomposes on exposure to acid fumes. Its solutions have a pH of about 8 to 9.5. One g dissolves in about 30 mL of water. Is slightly soluble in alcohol.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 3.0% of its weight.

Residue on ignition—Accurately weigh about 1 g, previously dried at 105° for 4 hours, and place it in a porcelain dish or crucible. Ignite carefully until well charred, cool, add 2 mL of sulfuric acid, and carefully ignite until the residue is white or practically so. Cool, add 0.5 mL of sulfuric acid and 1 mL of nitric acid, evaporate, and again ignite to constant weight: the weight of the sodium sulfate so obtained is between 20.0% and 24.0% of the weight of the dried specimen taken.

Sensitiveness—To 50 mL of carbon dioxide-free water add 0.1 mL of congo red solution (1 in 1000). The red color of the solution is changed to violet by the addition of 0.05 mL of 0.10 N hydrochloric acid and is restored by the subsequent addition of 0.05 mL of 0.10 N sodium hydroxide.

BRIEFING

Cyclohexanol, *USP 28* page 2811—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-26

Change to read:

Cyclohexanol, $C_6H_{12}O$—**100.16**—A clear liquid. ~~having a camphoraceous odor.~~

▲▲*USP29*
Freely soluble in water. Miscible with alcohol, with ethyl acetate, and with aromatic hydrocarbons.

Assay—When examined by gas-liquid chromatography, using suitable gas chromatographic apparatus and conditions, it shows a purity of not less than 98%.

Melting temperature: about 23°.

Specific gravity: about 0.962, at 20°.

BRIEFING

***o*-Dichlorobenzene,** *USP 28* page 2812—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-27

Change to read:

***o*-Dichlorobenzene,** $C_6H_4Cl_2$—**147.00**—Clear liquid, having a light yellowish–brown tint (about APHA 20). ~~and an aromatic odor.~~

▲▲*USP29*
Practically insoluble in water. Miscible with alcohol and with ether. Boils at about 180°.

Assay—When examined by gas–liquid chromatography, with the use of suitable apparatus and conditions, it shows a purity of not less than 98%.

Density: between 1.299 and 1.301.

Refractive index ⟨831⟩: between 1.548 and 1.550 at 25°.

Residue on evaporation—Evaporate 80 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 50 mg (0.005%).

Acidity—Add phenolphthalein TS to 25 mL of methanol, and titrate with 0.02 N alcoholic potassium hydroxide VS until a faint pink color persists for 15 seconds. Pipet 25 mL of test specimen into the solution, mix, avoiding exposure to the atmosphere, and titrate with 0.02 N alcoholic potassium hydroxide VS: not more than 2.2 mL is required to restore the pink color (about 0.005%).

BRIEFING

Dicyclohexylamine, *USP 28* page 2813—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-28

Change to read:

Dicyclohexylamine, $(C_6H_{11})_2NH$—**181.32**—Clear, strongly alkaline liquid. ~~having a faint, fishy odor.~~

▲▲*USP29*
Sparingly soluble in water. Miscible with common organic solvents. Density: 0.9104. Solidifies at –0.1°; melts at about 20°.

Assay—Accurately weigh about 400 mg in a tared, small weighing bottle equipped with a well-fitting closure. Transfer the stoppered bottle to a 250-mL beaker, add sufficient glacial acetic acid TS to cover the bottle, and open the bottle under the surface of the acid. Add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Each mL of 0.1 N perchloric acid is equivalent to 18.13 mg of $(C_6H_{11})_2NH$. Not less than 98% is found.

Specific gravity ⟨841⟩: between 0.911 and 0.917.

Boiling range (Reagent test): between 255° and 257°.

Water, *Method I* ⟨921⟩: not more than 0.5%.

BRIEFING

Diiodofluorescein, *USP 28* page 2814—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-29

Change to read:

Diiodofluorescein, $C_{20}H_{10}I_2O_5$—**584.10**—Orange-red ~~, odorless~~

▲▲*USP29*
powder. Slightly soluble in water; soluble in alcohol and in solutions of alkali hydroxides.

Residue on ignition—Ignite 200 mg with 5 drops of sulfuric acid: the weight of the residue does not exceed 1.0 mg (0.5%).

Sensitiveness—Accurately weigh about 100 mg of potassium iodide, previously dried at 105° to constant weight, and dissolve it in 50 mL of water. Add 1 mL of diiodofluorescein TS prepared from the test specimen and 1 mL of glacial acetic acid, and titrate with 0.1 N silver nitrate VS until the color of the precipitate changes from brownish red to a bluish red. The volume of 0.1 N silver nitrate consumed is not in excess of 0.10 mL over the calculated volume, based on the KI content of the dried potassium iodide determined as follows. Dissolve about 500 mg of potassium iodide, accurately weighed, in about 10 mL of water, and add 35 mL of hydrochloric acid and 5 mL of chloroform. Titrate with 0.05 M potassium iodate VS until the purple color of iodine disappears from the chloroform. Add the last portions of the iodate solution dropwise, agitating vigorously and continuously. After the chloroform has been decolorized, allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each mL of 0.05 M potassium iodate is equivalent to 16.60 mg of KI.

BRIEFING

1,2-Dimethoxyethane, *USP 28* page 2814—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-30

Change to read:

1,2-Dimethoxyethane, $C_4H_{10}O_2$—**90.12**—Clear, colorless liquid. ~~having a sharp, ethereal odor.~~

▲▲*USP29*
Miscible with water and with alcohol. Soluble in hydrocarbon solvents. *May form peroxides on standing*.

Boiling range (Reagent test)—Not less than 95% distils between 83° and 86°.

Refractive index ⟨831⟩: between 1.379 and 1.381, at 20°.

Acidity—To 20 mL add bromophenol blue TS, and titrate with 0.020 N sodium hydroxide: not more than 2.0 mL is consumed (about 0.015% as CH_3COOH).

Water, *Method I* ⟨921⟩: not more than 0.2%.

BRIEFING

Ethyl Cyanoacetate, *USP 28* page 2817—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-31

Change to read:

Ethyl Cyanoacetate, $CNCH_2COOC_2H_5$—**113.11**—Colorless to pale yellow liquid. ~~having a pleasant odor.~~

▲▲*USP29*
Slightly soluble in water. Miscible with alcohol and with ether. At atmospheric pressure it boils between 205° and 209°, with decomposition. At a pressure of 10 mm of mercury it distils at about 90°.

Specific gravity ⟨841⟩: between 1.057 and 1.062.

Acidity—Dissolve 2 mL in 25 mL of neutralized alcohol, add phenolphthalein TS, and titrate with 0.10 N sodium hydroxide: not more than 1.5 mL is required to produce a pink color.

BRIEFING

Ethylene Glycol, *USP 28* page 2818—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42098-32

Change to read:

Ethylene Glycol, $HOCH_2CH_2OH$—**62.07**—Clear, colorless, slightly viscous, hygroscopic ~~practically odorless~~

▲▲*USP29*
liquid. Slightly soluble in ether; practically insoluble in benzene. Miscible with water and with alcohol.

Specific gravity ⟨841⟩: about 1.11.

Boiling range (Reagent test): between 194° and 200°.

Residue on ignition—Evaporate 100 mL (110 g) in a tared evaporating dish over a flame until the vapors continue to burn after the flame is removed. Allow the vapors to burn until the specimen is consumed. Ignite at 800 ± 25° for 1 hour, cool, and weigh: the residue weighs not more than 5.5 mg (0.005%).

Acidity—Add 0.2 mL of phenol red TS to 50 mL of water, and titrate with 0.1 N sodium hydroxide to a red endpoint. Add 50 mL (55 g) of ethylene glycol, and titrate with 0.1 N sodium hydroxide: not more than 1 mL is required to restore the red color (0.01% as CH_3COOH).

Chloride (Reagent test)—A 4.5-mL (5-g) portion shows not more than 0.025 mg of Cl (5 ppm).

Water, *Method I* ⟨921⟩: not more than 0.20%.

BRIEFING

Ferric Ammonium Citrate, *USP 28* page 2818—See briefing under *Acetanilide*.

(HDQ: M. Marques) RTS—42098-33

Change to read:

Ferric Ammonium Citrate—Thin, transparent, garnet-red scales or granules or brownish-yellow powder. ~~odorless or having a slightly ammoniacal odor.~~

▲▲*USP29*
Is deliquescent and is affected by light. Very soluble in water; insoluble in alcohol.

Assay—Accurately weigh about 1 g, dissolve in 25 mL of water in a glass-stoppered flask, add 5 mL of hydrochloric acid and 4 g of potassium iodide, insert the stopper in the flask, and allow to stand in the dark for 15 minutes. Add 100 mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium thiosulfate is equivalent to 5.585 mg of Fe: between 16.5% and 18.5% is found.

Ferric citrate—To 250 mg dissolved in 25 mL of water add 1 mL of potassium ferrocyanide TS: no blue precipitate is formed.

Tartrate—Dissolve 1 g in 10 mL of water, add 1 mL of potassium hydroxide TS, boil to coagulate the ferric hydroxide, adding more potassium hydroxide TS, if necessary, to precipitate all of the iron, filter, and slightly acidify the filtrate with glacial acetic acid. Add 2 mL of glacial acetic acid, and allow to stand for 24 hours: no crystalline white precipitate is formed.

Lead ⟨251⟩—Dissolve 1.0 g in 30 mL of water, add 5 mL of dilute nitric acid (1 in 21), boil gently for 5 minutes, cool, and dilute with water to 50 mL: 20 mL of the solution shows not more than 0.008 mg of Pb (0.002%).

BRIEFING

Guaiacol, *USP 28* page 2820—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-1

Change to read:

Guaiacol *(o-Methoxyphenol)* $C_7H_8O_2$—**124.14**—Colorless to yellowish, refractive liquid. ~~having a characteristic odor.~~

▲▲*USP29*
Soluble in about 65 parts of water; soluble in sodium hydroxide solution; miscible with alcohol, with chloroform, with ether, and with glacial acetic acid.

Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying it: a 3-mm × 1.8-m stainless steel column containing liquid phase G16 on 60- to 80-mesh support S1A. Helium is the carrier gas, the injection port temperature is maintained at 180°, the column temperature is maintained at 200°, and the flame-ionization detector is maintained at 280°. The retention time is about 8 minutes.

Refractive index ⟨831⟩: between 1.5430 and 1.5450, at 20°.

BRIEFING

***n*-Heptane, Chromatographic,** *USP 28* page 2821—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-2

Change to read:

***n*-Heptane, Chromatographic**—Clear, colorless, volatile, flammable liquid consisting essentially of C_7H_{16}. ~~It has a characteristic odor.~~

▲▲*USP29*
Practically insoluble in water; soluble in absolute alcohol. Miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils. [NOTE—*n*-Heptane may require purification by passage through a column of silica gel, a ratio of about 25 g of the gel for each 100 mL of *n*-heptane being used, and subsequent fractional distillation.]

Boiling range (Reagent test): between 94.5° and 99.0°.

Spectral purity—Measure in a 1-cm cell at 250 nm, with a suitable spectrophotometer, against water as the blank: its absorbance is not more than 0.10.

Residue on evaporation—It meets the requirements of the test for *Residue on evaporation* under *Hexane, Solvent*.

BRIEFING

Hexamethyldisilazane, *USP 28* page 2821—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-3

Change to read:

Hexamethyldisilazane, $C_6H_{19}NSi_2$—**161.39**—Clear, colorless liquid. ~~, having a characteristic odor.~~

▲▲*USP29*
Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 95%. The following conditions have been found suitable for assaying the article: A 2-mm × 1.8-m glass column packed with phase G3 on support S1. Helium, flowing at a rate of about 40 mL per minute, is the carrier gas; the detector temperature is about 310°; the injection port temperature is about 100°; and the column temperature is programmed to start at 35°, hold for 5 minutes, then rise at a rate of 8° per minute to 200°. A flame-ionization detector is employed.

Residue after evaporation—Transfer 200 g to a tared dish, and evaporate on a steam bath to dryness. Dry the residue at 105° for 1 hour, cool, and weigh: not more than 0.0025% of residue is found.

BRIEFING

Hexane, Solvent, *USP 28* page 2821 and page 1045 of *PF* 30(3) [May–June 2004]—See briefing under *Acetanilide*.

(HDQ: M. Marques) RTS—42104-4

Change to read:

Hexane, Solvent ~~*(Petroleum Benzin; Petroleum Ether)*~~

■*(Petroleum Benzin; Petroleum Ether, Ligroin)*■1S (*USP28*)—Clear, volatile liquid. ~~having an ethereal or faint, petroleum-like odor.~~

▲▲*USP29*
Practically insoluble in water; soluble in absolute alcohol. Miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils.

Caution—It is dangerously flammable. Keep it away from flames, and store in tight containers in a cool place.

~~*Appearance and color*—Pour 100 mL, previously well-mixed in its original container, into a 100-mL color-comparison tube, and compare with a standard, in a similar tube, containing 2 mL of platinum-cobalt TS in similar volume: the two liquids are equally clear and free from suspended matter or sediment and when viewed across the columns by transmitted light, the test specimen is not darker in color than the standard.~~

~~*Odor*—Its odor is not disagreeable or suggestive of mercaptans or thiophene.~~

~~*Distilling range* (Reagent test)—Distil 100 mL: none distils below 30° and not less than 100% distils between 30° and 60°.~~

~~*Residue on evaporation*—Evaporate 150 mL (100 g) on a steam bath, and dry at 105° for 30 minutes: the residue weighs not more than 1 mg (0.001%).~~

~~*Acidity*—Shake 10 mL with 5 mL of water for 2 minutes, and allow the layers to separate: the water layer does not turn blue litmus red within 15 seconds.~~

~~*Heavy oils and fats*—Gradually pour 10 mL onto the center of a clean filter paper: there is no disagreeable odor and no greasy stain visible on the paper after it has stood for 30 minutes.~~

■Use ACS reagent grade Petroleum Ether.■1S (*USP28*)

BRIEFING

Inositol, *USP 28* page 2823—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-5

Change to read:

Inositol (*Hexahydroxycyclohexane*), $C_6H_6(OH)_6$—**180.16**—Fine, white crystals or a white, crystalline powder; ~~odorless,~~

▲▲*USP29*
stable in air. Its solutions are neutral to litmus. Optically inactive. One g dissolves in 5.7 mL of water. Slightly soluble in alcohol; insoluble in ether and in chloroform. Store in well-closed containers.

Melting range ⟨741⟩: between 223° and 226°.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

BRIEFING

Isopropylamine, *USP 28* page 2824—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-6

Change to read:

Isopropylamine (*2-Aminopropane*), $C_3H_7NH_2$—**59.11**—Clear, colorless, flammable liquid. ~~having a strong odor of ammonia.~~

▲▲*USP29*
Miscible with water, with alcohol, and with ether.

Assay—Transfer about 0.2 g, accurately weighed, to a suitable container, add 50 mL of water, and mix. Titrate with 0.1 N hydrochloric acid VS, using a mixture of methyl red TS and bromocresol green TS (1 : 5) as indicator. Each mL of 0.1 N hydrochloric acid is equivalent to 59.11 mg of C_3H_9N. Not less than 98% is found.

Boiling range (Reagent test)—Not less than 95% distils between 31° and 33°.

Refractive index ⟨831⟩: between 1.3743 and 1.3753, at 20°.

In-Process Revision

BRIEFING

Maleic Acid, *USP 28* page 2825—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-7

Change to read:

Maleic Acid, $C_4H_4O_4$—**116.07**—White ~~odorless,~~

▲▲*USP29*
crystalline powder. Soluble in 1.5 parts of water, in 2 parts of alcohol, and in 12 parts of ether.

Assay—Dissolve about 2 g, accurately weighed, in 100 mL of water and titrate with 1 N sodium hydroxide VS, using phenolphthalein TS as the indicator. Each mL of 1 N sodium hydroxide is equivalent to 58.04 mg of $C_4H_4O_4$: not less than 99% of $C_4H_4O_4$, calculated on the dried basis, is found.

Loss on drying—Dry it in vacuum over phosphorus pentoxide for 2 hours: it loses not more than 1.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

BRIEFING

Methyl Acetate, *USP 28* page 2826—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-8

Change to read:

Methyl Acetate, $C_3H_6O_2$—**74.08**—Colorless liquid. ~~having a characteristic odor.~~

▲▲*USP29*
Soluble in water. Miscible with alcohol and with ether.

Specific gravity ⟨841⟩: about 0.933.

Refractive index ⟨831⟩: between 1.3615 and 1.3625 at 20°.

Boiling range (Reagent test)—Not less than 95% distills between 57° and 58°.

BRIEFING

1-Naphthol, *USP 28* page 2828—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-12

Change to read:

1-Naphthol (*Alphanaphthol*), $C_{10}H_7OH$—**144.17**—Colorless or slightly pinkish crystals or crystalline powder. ~~having a characteristic odor.~~

▲▲*USP29*
Insoluble in water; soluble in alcohol, in benzene, and in ether.

Melting range ⟨741⟩: between 95° and 97°.

Solubility—Separate 1-g portions dissolve in alcohol and in benzene to yield solutions that are clear and colorless or nearly colorless.

Acidity—Shake 1 g with 50 mL of water occasionally during 15 minutes, and filter: the filtrate is neutral to litmus.

Residue on ignition (Reagent test): not more than 0.05%.

BRIEFING

2-Naphthol, *USP 28* page 2828—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-13

Change to read:

2-Naphthol (*Betanaphthol*), $C_{10}H_7OH$—**144.17**—White leaflets or crystalline powder. ~~having a faint, characteristic odor.~~

▲▲*USP29*
Discolors on exposure to light. Very slightly soluble in water; soluble in alcohol, in ether, in chloroform, and in solutions of alkali hydroxides.

Melting range ⟨741⟩: between 121° and 123°.

Solubility in alcohol—A solution of 1 g in 10 mL of alcohol is complete and colorless or practically so.

Residue on ignition (Reagent test): not more than 0.05%.

Acidity—Shake 1 g with 50 mL of water occasionally during 15 minutes, and filter: the filtrate is neutral to litmus.

1-Naphthol—Boil 100 mg with 10 mL of water until dissolved, cool, and filter. Add to the filtrate 0.3 mL of 1 N sodium hydroxide and 0.3 mL of 0.1 N iodine: no violet color is produced.

Insoluble in ammonia (naphthalene, etc.)—Shake 500 mg with 30 mL of ammonia TS: the 2-naphthol dissolves completely and the solution is not darker than pale yellow.

BRIEFING

5-Nitro-1,10-phenanthroline, *USP 28* page 2829—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-14

Change to read:

5-Nitro-1,10-phenanthroline, $C_{12}H_7N_3O_2$—**225.20**—White~~,~~ ~~odorless~~

▲▲*USP29*
powder. Soluble in water.

Melting range ⟨741⟩: between 198° and 200°.

Suitability as redox indicator—Dissolve 25 mg in a minimum volume of diluted sulfuric acid, add 10 mg of ferrous sulfate, and dilute with water to 100 mL: the solution is deep red in color and exhibits an absorption maximum at 510 nm. To 1.0 mL of the solution add 1.0 mL of 0.01 M ceric sulfate: the red color is discharged.

BRIEFING

Nonylphenoxypoly(ethyleneoxy)ethanol, *USP 28* page 2829—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-15

Change to read:

Nonylphenoxypoly(ethyleneoxy)ethanol—Clear, viscous, pale yellow liquid. ~~having an aromatic odor.~~

▲▲*USP29*
May exhibit slight solidification on cooling; warming with agitation will restore to original condition. Density: about 1.06. Soluble in alcohol, in xylene, and in water. Suitable for use in gas–liquid chromatography.

[NOTE—A suitable grade is "Igepal CO 710," available from General Aniline and Film Corp., 140 West 51st St., New York, NY 10020.]

BRIEFING

***Para*-aminobenzoic Acid,** *USP 28* page 2831—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-17

Change to read:

***Para*-aminobenzoic Acid** (*p-Aminobenzoic Acid*), $H_2NC_6H_4COOH$—**137.14**—White or slightly yellow ~~odorless~~

▲▲*USP29*
crystals or crystalline powder, becoming discolored on exposure to air or light. One g dissolves in 170 mL of water, in 9 mL of boiling water, in 8 mL of alcohol, and in 50 mL of ether. Freely soluble in solutions of alkali hydroxides and carbonates; soluble in warm glycerin; sparingly soluble in diluted hydrochloric acid; slightly soluble in chloroform. Store in tight, light-resistant containers.

Assay—Accurately weigh about 300 mg, previously dried at 105° for 2 hours, and transfer to a beaker or casserole. Add 5 mL of hydrochloric acid and 50 mL of water, and stir until dissolved. Cool to about 15°, add about 25 g of crushed ice, and slowly titrate with 0.1 M sodium nitrite VS until a glass rod dipped into the titrated solution produces an immediate blue ring when touched to starch iodide paper. When the titration is complete, the endpoint is reproducible after the mixture has been allowed to stand for 1 minute. Each mL of 0.1 M sodium nitrite is equivalent to 13.71 mg of $C_7H_7NO_2$. Not less than 98.5% is found.

Melting range ⟨741⟩: between 186° and 189°.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.2% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

BRIEFING

Paraformaldehyde, *USP 28* page 2831—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-18

Change to read:

Paraformaldehyde, $(CH_2O)_n$—Fine, white powder. ~~having the characteristic odor of formaldehyde.~~

▲▲*USP29*
Assay—Transfer about 1 g, accurately weighed, to a 250-mL conical flask containing 50.0 mL of 1 N sodium hydroxide VS, and mix by swirling. Immediately, and slowly, add 50 mL of hydrogen peroxide TS, previously neutralized to bromothymol blue, through a small funnel placed in the neck of the flask. After the reaction moderates, rinse the funnel and inner wall of the flask with water, allow the solution to stand for 30 minutes, add bromothymol blue TS, and titrate the excess alkali with 1 N sulfuric acid VS. Each mL of 1 N sodium hydroxide is equivalent to 30.03 mg of HCHO: not less than 95% is found.

Residue on ignition: not more than 0.1%.

In-Process Revision

Solubility in ammonia—Dissolve 5 g in 50 mL of ammonia TS: a practically clear, colorless solution results.

Reaction—Shake 1 g with 20 mL of water for about 1 minute, and filter: the filtrate is neutral to litmus.

BRIEFING

Propionic Anhydride, *USP 28* page 2835—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-19

Change to read:

Propionic Anhydride, $C_6H_{10}O_3$—**130.14**—Colorless liquid. ~~having a pungent odor.~~

▲▲*USP29*
Is decomposed by water. Soluble in methanol, in alcohol, in ether, and in chloroform.

Assay—Accurately weigh about 350 mg into a tared, glass-stoppered flask containing 50 mL of dimethylformamide previously neutralized to the thymol blue endpoint with 0.1 N sodium methoxide in methanol VS. Titrate with 0.1 N sodium methoxide in methanol VS to the thymol blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium methoxide is equivalent to 13.014 mg of $C_6H_{10}O_3$. Not less than 97.0% is found.

Refractive index ⟨831⟩: between 1.4035 and 1.4045 at 20°.

BRIEFING

Pyrrole, *USP 28* page 2836—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-21

Change to read:

Pyrrole, C_4H_5N—**67.09**—Clear liquid, colorless when freshly distilled, becoming yellow in a few days. ~~Has a characteristic odor.~~

▲▲*USP29*
Specific gravity: about 0.94. Insoluble in water; soluble in alcohol, in benzene, and in ether.

Boiling range (Reagent test)—Not less than 90% distills between 128° and 132°.

BRIEFING

Rose Bengal Sodium, *USP 28* page 2837—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-22

Change to read:

Rose Bengal Sodium (*Disodium Salt of 4,5,6,7-Tetrachloro-2′,4′,5′,7′-tetraiodofluorescein*), $C_{20}H_2Cl_4I_4Na_2O_5$—**1017.64**—Fine, rose-colored crystals or crystalline powder. ~~Is practically odorless.~~

▲▲*USP29*
Soluble in water.

NOTE—Render commercially available material suitably pure by the following treatment. Dissolve 8 g in 200 mL of water, and adjust to a pH between 10 and 11, using short-range pH indicator paper. Add 200 mL of acetone, while stirring gently, then add dilute hydrochloric acid (1 in 10), while continuing to stir, until the pH of the solution reaches 4.0. Add 400 mL more of water, with stirring, and continue the stirring for 5 minutes. Filter the crystals on a filtering funnel, and return the crystals to the beaker used for crystallization. Recrystallize three more times in the same manner, and dry the crystals at 110° for 12 hours. Store in an amber bottle in a refrigerator at a temperature between 2° and 8°. Prepare this reagent fresh monthly.

Chromatographic purity—Dissolve 100 mg of rose bengal sodium, prepared as described above, in 100 mL of water, and apply 10 µL of the solution on suitable chromatographic paper. Develop the chromatogram by ascending chromatography, using a mixture of 1 part of dilute alcohol (1 in 4) and 1 part of dilute stronger ammonia water (1 in 12). Examine the chromatogram in daylight and under UV light (360 nm): no colored or fluorescent spot is visible other than the rose bengal sodium spot.

[NOTE—A suitable grade is available commercially as "Silica Gel H".]

BRIEFING

Silver Oxide, *USP 28* page 2839—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-23

Change to read:

Silver Oxide, Ag_2O—**231.74**—Brownish-black, heavy ~~odorless~~

▲▲*USP29*
powder. Slowly decomposes on exposure to light. Absorbs carbon dioxide when moist. Practically insoluble in water; freely soluble in dilute nitric acid and in ammonia; insoluble in alcohol. Store in well-closed containers; do not expose to ammonia fumes or easily oxidizable substances.

Assay—Dissolve about 500 mg, previously dried at 120° for 3 hours and accurately weighed, in a mixture of 20 mL of water and 5 mL of nitric acid. Dilute with 100 mL of water, add 2 mL of ferric

ammonium sulfate TS, and titrate with 0.1 N ammonium thiocyanate VS to a permanent reddish-brown color. Each mL of 0.1 N ammonium thiocyanate is equivalent to 11.59 mg of Ag_2O: not less than 99.7% of Ag_2O is found.

Loss on drying—Dry it at 120° for 3 hours: it loses not more than 0.25% of its weight.

Nitrate—To 500 mg add 30 mg of sodium carbonate and 2 mL of phenoldisulfonic acid TS, mix, and heat on a steam bath for 15 minutes. Cool, *cautiously* add 20 mL of water, render alkaline with ammonia TS, and dilute with water to 30 mL: any color produced by the test solution is not darker than that produced in a control containing 0.01 mg of NO_3 (0.002%).

Substances insoluble in nitric acid—Dissolve 5 g in a mixture of 5 mL of nitric acid and 10 mL of water, dilute with water to about 65 mL, and filter any undissolved residue on a tared filtering crucible (retain the filtrate for the test for *Substances not precipitated by hydrochloric acid*). Wash the crucible with water until the last washing shows no opalescence with 1 drop of hydrochloric acid, and dry at 105° to constant weight: the residue weighs not more than 1 mg (0.02%).

Substances not precipitated by hydrochloric acid—Dilute the filtrate obtained in the test for *Substances insoluble in nitric acid* with water to 250 mL, heat to boiling, and add, dropwise, sufficient hydrochloric acid to precipitate all of the silver (about 5 mL), avoiding any great excess. Cool, dilute with water to 300 mL, and allow to stand overnight. Filter, evaporate 200 mL of the filtrate in a suitable tared porcelain dish to dryness, and ignite: the residue weighs not more than 1.7 mg (0.05%).

Alkalinity—Heat 2 g with 40 mL of water on a steam bath for 15 minutes, cool, and dilute with water to 50 mL. Filter, discarding the first 10 mL of the filtrate. To 25 mL of the subsequent filtrate add 2 drops of phenolphthalein TS, and titrate with 0.02 N hydrochloric acid VS to the disappearance of any pink color: not more than 0.20 mL is required (0.016% as NaOH).

BRIEFING

Sodium Arsenite, *USP 28* page 2839—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-24

Change to read:

Sodium Arsenite, $NaAsO_2$—**129.91**—White, crystalline~~, odorless~~

▲▲*USP29*
powder. Soluble in water; slightly soluble in alcohol.

Assay—Transfer about 5.5 g, accurately weighed, to a 500-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Pipet 25 mL of this solution into a suitable container, add 50 mL of water and 5 g of dibasic sodium phosphate, swirl to dissolve, and titrate with 0.1 N iodine VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N iodine is equivalent to 3.746 mg of As. Between 57.0% and 60.5% is found (equivalent to 98.8% to 104.9% of $NaAsO_2$).

Chloride (Reagent test)—One g shows not more than 0.10 mg of Cl (0.01%).

Heavy metals—Dissolve 200 mg in 8 mL of dilute hydrochloric acid (3 in 8), and evaporate on a steam bath to dryness. Dissolve the residue in 5 mL of dilute hydrochloric acid (2 in 5), and again evaporate to dryness. Dissolve the residue in 10 mL of water, and add 2 mL of diluted acetic acid and 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%).

Iron—Dissolve 1 g in 20 mL of dilute hydrochloric acid (1 in 5), and add, dropwise, a slight excess of bromine TS. Boil the solution to remove the excess bromine, cool, dilute with water to 40 mL, and add 10 mL of ammonium thiocyanate solution (3 in 10). Any red color produced is not darker than that of a control containing 0.02 mg of added Fe (0.02%).

Sulfide—Dissolve 1 g in 20 mL of water, and add 5 drops of lead acetate TS: no brown color is produced (about 0.0005%).

Sulfate (Reagent test, *Method II*)—Dissolve 5 g in 100 mL of water, add methyl orange TS, neutralize with 1 N hydrochloric acid, add 3 mL of the acid in excess, and filter: the filtrate yields not more than 3 mg of residue (0.02%).

BRIEFING

Sodium Chromate, *USP 28* page 2840—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-26

Change to read:

Sodium Chromate, $Na_2CrO_4 \cdot 4H_2O$—**234.03**—Lemon-yellow ~~odorless~~

▲▲*USP29*
crystals. Soluble in water.

Assay—Accurately weigh about 300 mg, and dissolve in 10 mL of water contained in a 500-mL flask. Add 3 g of potassium iodide and 10 mL of diluted sulfuric acid, and dilute with 350 mL of oxygen-free and carbon dioxide-free water. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate consumed is equivalent to 7.802 mg of $Na_2CrO_4 \cdot 4H_2O$. Not less than 99% is found.

Insoluble matter (Reagent test): not more than 1 mg, from 20 g dissolved in 150 mL of water (0.005%).

Aluminum—Dissolve 20 g in 140 mL of water, filter, and add 5 mL of glacial acetic acid to the filtrate. Add stronger ammonia water until alkaline, and digest for 2 hours on a steam bath. Filter through hardened filter paper, wash thoroughly, ignite, and weigh: the residue weighs not more than 0.8 mg (0.002%).

Calcium—Determine as directed in the test for calcium for ACS reagent grade Potassium Chromate (0.005%).

Chloride—Determine as directed in the test for chloride for ACS reagent grade Potassium Chromate (about 0.005%).

Sulfate—Determine as directed in the test for sulfate for ACS reagent grade Potassium Dichromate, but add 4.5 mL of hydrochloric acid to the water used to dissolve the test specimen: the residue weighs not more than 2.4 mg (0.01%).

In-Process Revision

BRIEFING

Sodium Glycocholate, *USP 28* page 2841—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-27

Change to read:

Sodium Glycocholate, $C_{26}H_{42}NNaO_6$—**487.60**—White to tan ~~odorless or practically odorless~~

▲▲*USP29*
powder. Is hygroscopic. Freely soluble in water and in alcohol.

Specific rotation ⟨781⟩: between +28° and +31°, calculated on the dried basis (it is rendered anhydrous by drying at 100° for 2 hours), determined at 20° in a solution containing 10 mg per mL.

Nitrogen, *Method I* ⟨461⟩: between 2.6% and 3.2% of N is found, calculated on the dried basis.

BRIEFING

Sodium 1-Hexanesulfonate Monohydrate. This new reagent is used to prepare the *Buffer solution* in the test for *Chromatographic purity* and in the *Assay* under *Methscopolamine Bromide,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41998-2

Add the following:

▲**Sodium 1-Hexanesulfonate Monohydrate,** $C_6H_{13}NaO_3S \cdot H_2O$—**206.23** [*2832-45-3*]—Use a suitable grade.▲*USP29*

BRIEFING

Tetramethylammonium Hydroxide, *USP 28* page 2846—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-30

Change to read:

Tetramethylammonium Hydroxide, $(CH_3)_4NOH$—**91.15**—Available as an approximately 10% or approximately 25% aqueous solution, or as the crystalline pentahydrate. Is clear and colorless. ~~and has a strong, ammonia-like odor.~~

▲▲*USP29*
Tetramethylammonium hydroxide is a stronger base than ammonia, and rapidly absorbs carbon dioxide from the air. Store in tight containers.

Assay—Accurately weigh a glass-stoppered flask containing about 15 mL of water. Add a quantity of a solution of tetramethylammonium hydroxide, equivalent to about 200 mg of $(CH_3)_4NOH$, and again weigh. Add methyl red TS, and titrate the solution with 0.1 N hydrochloric acid VS: each mL of 0.1 N acid is equivalent to 9.115 mg of $(CH_3)_4NOH$.

Residue on evaporation—Evaporate 5 mL of solution on a steam bath, and dry at 105° for 1 hour: the weight of the residue is equivalent to not more than 0.02% of the weight of the test specimen.

Ammonia and other amines—Accurately weigh a quantity of solution, corresponding to about 300 mg of $(CH_3)_4NOH$, in a low-form weighing bottle tared with 5 mL of water. Add a slight excess of 1 N hydrochloric acid (about 4 mL), evaporate on a steam bath to dryness, and dry at 105° for 2 hours: the weight of the tetramethylammonium chloride so obtained, multiplied by 0.8317, represents the quantity, in mg, of $(CH_3)_4NOH$ in the portion of test specimen taken and corresponds to within 0.2% above or below that found in the *Assay.*

BRIEFING

Thioglycolic Acid, *USP 28* page 2846—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-31

Change to read:

Thioglycolic Acid (*Thioglycolic Acid*), $HSCH_2COOH$—**92.12**—A colorless or nearly colorless liquid. ~~having a strong, unpleasant odor.~~

▲▲*USP29*
Miscible with water. Soluble in alcohol.

Residue on ignition ⟨Reagent test⟩: not more than 0.1%.

Solubility—A solution of 1 mL in 10 mL of water is clear and colorless.

Sensitiveness—Mix 1 mL with 2 mL of stronger ammonia water, and dilute with water to 20 mL. Add 1 mL of this solution to a mixture of 20 mL of water and 0.1 mL of dilute ferric chloride TS (1 in 100), then add 5 mL of ammonia TS: a distinct pink color is produced.

BRIEFING

Thymol, *USP 28* page 2847—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-32

Change to read:

Thymol, $C_6H_3[CH_3][OH][CH(CH_3)_2]1,3,4$—**150.22**—Colorless, often large, crystals, or a white, crystalline powder. ~~having an aromatic, thyme-like odor.~~

▲ ▲*USP29*
Is affected by light. Has greater density than water, but when liquefied by fusion is less dense than water. Its alcohol solutions are neutral to litmus. One g dissolves in about 1000 mL of water, in 1 mL of alcohol, in 1 mL of chloroform, in 1.5 mL of ether, and in about 2 mL of olive oil. Soluble in glacial acetic acid and in fixed or volatile oils. Store in tight, light-resistant containers.

Melting range ⟨741⟩: between 48° and 51°, but when melted it remains liquid at a considerably lower temperature.

Nonvolatile matter—Volatilize 2 g on a steam bath, and dry at 105° to constant weight: the residue weighs not more than 1 mg (0.05%).

BRIEFING

***n*-Tricosane,** *USP 28* page 2848—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-33

Change to read:

***n*-Tricosane,** $C_{23}H_{48}$—**324.63**—Colorless or white, more or less translucent mass, showing a crystalline structure. ~~Odorless, or practically so.~~

▲ ▲*USP29*
Has a slightly greasy feel. Insoluble in water and in alcohol; soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils; slightly soluble in dehydrated alcohol. Boils at about 380°.

Melting range ⟨741⟩: between 47° and 49°.

Suitability—Determine its suitability for use in the test for *Related compounds* under *Propoxyphene Hydrochloride* (USP monograph) as follows. Dissolve a suitable quantity in chloroform to yield a solution containing 20 µg per mL. Following the directions given in the test for *Related compounds* under *Propoxyphene Hydrochloride,* inject a suitable volume of the solution into the chromatograph, and record the chromatogram. Concomitantly record the chromatogram from the *Standard preparation* prepared as directed in the test for *Related compounds:* only one main peak is obtained from the *n*-tricosane solution, and no minor peaks are observed at, or near, the peak positions obtained for propoxyphene, acetoxy, or carbinol in the chromatogram from the *Standard preparation*.

BRIEFING

Triethylamine, *USP 28* page 2848—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-34

Change to read:

Triethylamine, $(C_2H_5)_3N$—**101.19**—Colorless liquid. ~~having a strong, ammoniacal odor.~~

▲ ▲*USP29*
Slightly soluble in water. Miscible with alcohol, with ether, and with cold water. Store in well-closed containers.

Boiling range (Reagent test): between 89° and 90°.

Absorbance—To 1 mL in a 50-mL volumetric flask add 10 mL of methanol and 1 mL of hydrochloric acid, and add chloroform to volume. The absorbance of this solution, determined at the wavelength of maximum absorbance at about 285 nm, with a suitable spectrophotometer, does not exceed 0.01. [NOTE—If the absorbance exceeds 0.01, purify the triethylamine as follows. Reflux 100 mL with 20 mL of water and 2 g of sodium hydrosulfite for not less than 8 hours, wash with water, dry by refluxing, using a Dean-Stark trap, and distill, collecting only the first 75 mL of the filtrate. Store over anhydrous sodium carbonate or anhydrous potassium carbonate.]

BRIEFING

2,4,6-Trimethylpyridine, *USP 28* page 2849—See briefing under *Acetanilide.*

(HDQ: M. Marques) RTS—42104-35

Change to read:

2,4,6-Trimethylpyridine (*5-Collidine*), $C_8H_{11}N$—**121.18**—Clear, colorless liquid. ~~having an aromatic odor.~~

▲ ▲*USP29*
Soluble in cold water and less soluble in hot water; soluble in alcohol, in chloroform, and in methanol. Miscible with ether.

Assay—Inject an appropriate test specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩), helium being used as a carrier gas. The following conditions have been found suitable: a 3-mm × 1.85-m stainless steel column containing phase G16 on support S1A; the injection port, column, and detector temperatures are maintained at 180°, 165°, and 270°, respectively, and a flame-ionization detector is used. The area of the $C_8H_{11}N$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.4970 and 1.4990, at 20°.

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869 and page 120 of *PF* 31(1) [Jan.–Feb. 2005].

(HDQ) RTS—40316-2

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:	
■Acetaminophen Tablets, Extended-Release	$T_{■1S}$ (*USP28*)
Add the following:	
■Benazepril Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Bismuth Subsalicylate Tablets	$T_{■2S}$ (*USP28*)
Add the following:	
■Cefaclor Tablets	$T_{■2S}$ (*USP28*)
Add the following:	
■Chromium Picolinate Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Clarithromycin Tablets, Extended-Release	$W_{■2S}$ (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Clopidogrel Tablets	$W_{■1S}$ (*USP28*)
Add the following:	
■Black Cohosh Tablets	T, $LR_{■2S}$ (*USP28*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Diethylstilbestrol Diphosphate Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Ergoloid Mesylates Tablets Sublingual	T, $LR_{■1S}$ (*USP28*)
Add the following:	
■Ergotamine Tartrate Tablets, Sublingual	W, $LR_{■1S}$ (*USP28*)
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Etodolac Tablets, Extended-Release	$W_{■1S}$ (*USP28*)
Add the following:	
■Fexofenadine Hydrochloride Capsules	T, $LR_{■1S}$ (*USP28*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	$W_{■2S}$ (*USP28*)
Add the following:	
■Fluoxetine Capsules, Delayed-Release	$T_{■1S}$ (*USP28*)
Add the following:	
■Fluvastatin Capsules	T, $LR_{■1S}$ (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Fosinopril Sodium Tablets	$T_{■2S}$ *(USP28)*
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	$T_{■2S}$ *(USP28)*
Add the following:	
■Gabapentin Capsules	$W_{■2S}$ *(USP28)*
Add the following:	
■Ginkgo Capsules	T, $LR_{■2S}$ *(USP28)*
Add the following:	
■Ginkgo Tablets	T, $LR_{■2S}$ *(USP28)*
Change to read:	
▲Asian Ginseng Capsules	T~~, LR~~ ■2S *(USP28)* ▲*USP28*
Add the following:	
■Indinavir Sulfate Capsules	$T_{■2S}$ *(USP28)*
Add the following:	
■Irbesartan Tablets	$W_{■2S}$ *(USP28)*
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	$W_{■2S}$ *(USP28)*
Add the following:	
■Isosorbide Mononitrate Tablets	$T_{■2S}$ *(USP28)*
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	$T_{■2S}$ *(USP28)*
Add the following:	
■Lysine Hydrochloride Tablets	$W_{■2S}$ *(USP28)*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Metformin Hydrochloride Tablets	$T_{■1S}$ *(USP28)*
Add the following:	
■Mirtazapine Tablets	T, $LR_{■1S}$ *(USP28)*
Add the following:	
■Modafinil Tablets	$T_{■2S}$ *(USP28)*
Add the following:	
■Naproxen Tablets, Delayed-Release	$W_{■1S}$ *(USP28)*
Add the following:	
■Nitroglycerin Tablets, Sublingual	$T_{■1S}$ *(USP28)*
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	$W_{■2S}$ *(USP28)*
Add the following:	
■Oxaprozin Tablets	T, $LR_{■2S}$ *(USP28)*
Add the following:	
■Pygeum Capsules	$T_{■1S}$ *(USP28)*
Add the following:	
■Quinapril Tablets	$W_{■2S}$ *(USP28)*
Add the following:	
■Stavudine Capsules	$T_{■1S}$ *(USP28)*
Add the following:	
▲Tizanidine Tablets	$T_{▲USP29}$
Add the following:	
■Tolcapone Tablets	$T_{■1S}$ *(USP28)*
Add the following:	
■Valerian Capsules	T, $LR_{■2S}$ *(USP28)*

In-Process Revision

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■2S *(USP28)*
Add the following:	
▲Zinc Sulfate Tablets	W▲*USP29*

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1542 of *PF* 28(5) [Sept.–Oct. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 267 of *PF* 29(1) [Jan.–Feb. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 2057 of *PF* 29(6) [Nov.–Dec. 2003], page 1050 of *PF* 30(3) [May–June 2004], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], and page 122 of *PF* 31(1) [Jan.–Feb. 2005].

(HDQ) RTS—37475-1; 37658-1; 41493-3; 41078-1; 41869-1; 41869-2; 42051-1; 41441-1

Add the following:

▲**Ademetionine Disulfate Tosylate:** White powder. Freely soluble in water.▲*USP29*

Add the following:

▲**Potassium Bromide:** White, crystalline powder or colorless, cubical crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.▲*USP29*

Add the following:

▲**Propylene Glycol Dilaurate:** Clear, oily liquid at 20°. Colorless or slightly yellow. Very soluble in alcohol, in methanol, and in methylene chloride; practically insoluble in water.▲*NF24*

Add the following:

▲**Propylene Glycol Monolaurate:** Clear, oily liquid at 20°. Colorless or slightly yellow. Very soluble in alcohol, in methanol, and in methylene chloride; practically insoluble in water.▲*NF24*

Add the following:

▲**Sodium Bromide:** White, crystalline powder or colorless, cubical crystals. Freely soluble in water; soluble in alcohol.▲*USP29*

Add the following:

▲**Tizanidine Hydrochloride:** Almost white to slightly yellow crystalline powder. Slightly soluble in water and in methanol.▲*USP29*

Add the following:

▲**Tramadol Hydrochloride:** White, crystalline powder. Freely soluble in water and in methanol; very slightly soluble in acetone.▲*USP29*

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

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Preservation, Packaging, Storage, and Labeling—See PF Vol. 30 No. 5, page 1574.

USP MONOGRAPHS

Acepromazine Maleate—See PF Vol. 29 No. 6, page 1832.
Acepromazine Maleate Injection—See PF Vol. 30 No. 4, page 1161.
Acetaminophen Extended-Release Tablets—See PF Vol. 30 No. 4, page 1161.
Acetaminophen Oral Suspension—See PF Vol. 30 No. 5, page 1579.
Acetaminophen and Aspirin Tablets—See PF Vol. 30 No. 1, page 41.
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 30 No. 1, page 43.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—See PF Vol. 30 No. 1, page 42.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 30 No. 1, page 44.
Acetaminophen and Codeine Phosphate Capsules—See PF Vol. 30 No. 1, page 45.
Acetaminophen and Diphenhydramine Citrate Tablets—See PF Vol. 30 No. 1, page 47.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 30 No. 1, page 47.
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 30 No. 1, page 48.
Acetohydroxamic Acid—See PF Vol. 30 No. 5, page 1579.
Acetohydroxamic Acid Tablets—See PF Vol. 30 No. 1, page 49.
Acyclovir—See PF Vol. 30 No. 5, page 1580.
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Albuterol Tablets—See PF Vol. 31 No. 1, page 40.
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Alendronate Sodium Tablets—See PF Vol. 28 No. 3, page 740.
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Allopurinol—See PF Vol. 28 No. 5, page 1386.
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Alumina, Magnesia, and Calcium Carbonate Tablets—See PF Vol. 29 No. 6, page 1835.
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets—See PF Vol. 29 No. 6, page 1836.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets—See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, and Simethicone Tablets—See PF Vol. 29 No. 6, page 1841.
Alumina, Magnesia, and Simethicone Chewable Tablets—See PF Vol. 29 No. 6, page 1842.
Amantadine Hydrochloride Capsules—See PF Vol. 30 No. 1, page 51.
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Amifostine for Injection—See PF Vol. 30 No. 6, page 1976.
Aminocaproic Acid—See PF Vol. 29 No. 5, page 1414.
Aminopentamide Sulfate—See PF Vol. 30 No. 4, page 1163.
Aminophylline—See PF Vol. 29 No. 5, page 1414.
Aminosalicylate Sodium Tablets—See PF Vol. 30 No. 1, page 53.
Amitriptyline Hydrochloride—See PF Vol. 29 No. 6, page 1844.
Ammonium Chloride—See PF Vol. 29 No. 5, page 1415.
Ammonium Molybdate—See PF Vol. 29 No. 5, page 1416.
Amoxicillin Capsules—See PF Vol. 30 No. 5, page 1583.
Amoxicillin Tablets—See PF Vol. 30 No. 6, page 1977.
Amphetamine Sulfate—See PF Vol. 30 No. 3, page 807.
Amphetamine Sulfate Tablets—See PF Vol. 30 No. 1, page 54.
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Amphotericin B Topical Emulsion—See PF Vol. 30 No. 2, page 445.
Ampicillin—See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules—See PF Vol. 30 No. 1, page 55.
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Anecortave Acetate—See PF Vol. 30 No. 2, page 445.
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Anileridine—See PF Vol. 29 No. 6, page 1846.
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L-Asparagine—See PF Vol. 29 No. 3, page 687.
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Atenolol—See PF Vol. 29 No. 5, page 1416.
Atenolol Tablets—See PF Vol. 29 No. 1, page 49.
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Atracurium Besylate Injection—See PF Vol. 30 No. 3, page 808.
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Betamethasone Sodium Phosphate—See PF Vol. 30 No. 4, page 1166.
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Diclofenac Sodium Delayed-Release Tablets (Harmonization)—See PF Vol. 31 No. 1, page 148.
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Dicyclomine Hydrochloride Tablets—See PF Vol. 30 No. 3, page 834.
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Diethylstilbestrol—See PF Vol. 29 No. 5, page 1463.
Diethylstilbestrol Diphosphate Tablets—See PF Vol. 30 No. 4, page 1187.
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Edetate Disodium—See PF Vol. 29 No. 5, page 1474.
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Ergotamine Tartrate and Caffeine Suppositories—See PF Vol. 30 No. 6, page 1988.
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1,2-Dioleoyl-3-linoleoyl-rac-glycerol—See PF Vol. 28 No. 3, page 849.
Direct Red 80—See PF Vol. 30 No. 4, page 1390.
Disodium Arsenate—See PF Vol. 28 No. 4, page 1305.
Ether, Peroxide-Free—See PF Vol. 30 No. 4, page 1390.
Ethidium Bromide—See PF Vol. 27 No. 6, page 3366.
Fast Green FCF—See PF Vol. 30 No. 4, page 1391.
Formamide, Anhydrous—See PF Vol. 27 No. 5, page 3115.
L-Glutamic Acid—See PF Vol. 27 No. 6, page 3366.
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Guanidine Isothiocyanate—See PF Vol. 27 No. 6, page 3366.
Heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin—See PF Vol. 30 No. 6, page 2169.
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2′-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5′-bi-1*H*-benzimidazole Trihydrochloride Pentahydrate—See PF Vol. 30 No. 4, page 1391.
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Footnote 113—See PF Vol. 30 No. 2, page 648.
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REFERENCE TABLES

Container Specifications for Capsules and Tablets—See PF Vol. 26 No. 4, page 1133; PF Vol. 26 No. 5, page 1384; 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. 29 No. 1, page 266; PF Vol. 29 No. 2, page 508; PF Vol. 29 No. 4, page 1262; PF Vol. 29 No. 5, page 1683; PF Vol. 29 No. 6, page 2055; PF Vol. 30 No. 2, page 648; PF Vol. 30 No. 3, page 1048; PF Vol. 30 No. 4, page 1404; PF Vol. 30 No. 5, page 1821; PF Vol. 30 No. 6, page 2181; PF Vol. 31 No. 1, page 120.
Description and Relative Solubility of USP and NF Articles—See PF Vol. 24 No. 5, page 7017; PF Vol. 25 No. 6, page 9254; PF Vol. 26 No. 4, page 1135; PF Vol. 27 No. 1, page 1907; PF Vol. 28 No. 2, page 554; 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. 3, page 812; PF Vol. 29 No.

4, page 1262; PF Vol. 29 No. 5, page 1684; PF Vol. 29 No. 6, page 2057; PF Vol. 30 No. 3, page 1050; PF Vol. 30 No. 4, page 1405; PF Vol. 30 No. 5, page 1822; PF Vol. 30 No. 6, page 2183; PF Vol. 31 No. 1, page 122.

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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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Albendazole Oral Suspension—*Labeling*	29	4	991
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Doxycycline Hyclate—*Content of ethanol*	30	3	836
Fluoxetine Hydrochloride—*USP Reference standards, Related compounds*	30	3	848
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Leuprolide Acetate Injection (new)—*Preview*	25	5	8722
Oxandrolone—*Related compounds*	30	1	148
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	28	2	360
†Terbutaline Sulfate Inhalation Aerosol (entire submission)	26	3	753
Valproic Acid Injection (new)—*Preview*	26	4	939
Dietary Supplements Monographs			
Shark Liver Oil (new)—*Preview*	26	6	1643
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USP Fluoxetine Related Compound B Solution RS	30	4	1338
†*USP Tazobactam Sodium RS*	29	3	711
⟨601⟩ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers—*Harmonization*	28	2	584
⟨621⟩ Chromatography—*Chromatographic Reagents, Phases* (Docosahexaenoic Acid)	29	6	2023
⟨776⟩ Optical Microscopy—*Harmonization*	28	2	606
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⟨811⟩ Powder Fineness (entire submission)	28	2	611
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⟨1174⟩ Powder Flow (new)—*Harmonization*	28	2	618
⟨1198⟩ Standardized Imprint Codes for Solid Oral Dosage Forms (new)—*Preview*	28	1	152
†⟨1225⟩ Validation of Compendial Methods—*Validation—Ruggedness*	30	4	1382
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Pentadecanoic Acid Methyl Ester (added)—*Preview*	26	6	1622
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Docosahexaenoic Acid (new)—*Preview*	26	6	1648
Docosahexaenoic Acid Capsules (new)—*Preview*	26	6	1651
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†New cancellations in *PF* 31(2).

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

Anhydrous Citric Acid, *USP 28* page 483 and page 1851 in *PF* 30(5) [Sept.–Oct. 2004]. The test for *Organic volatile impurities* is omitted to comply with the Stage 6 Harmonization Draft. It is proposed to implement the revision via the *Fourth Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of Aug. 1, 2005.

(EMC: J. Lane) RTS—42152-1

Add the following:

■**Packaging and storage**—Preserve in tight containers. No storage requirements specified.■2S (*USP28*)

Delete the following:

•~~**Organic volatile impurities,** *Method IV* ⟨467⟩**: meets the requirements.**~~•4

BRIEFING

Citric Acid Monohydrate, *USP 28* page 485 and page 1854 in *PF* 30(5) [Sept.–Oct. 2004]. The preparation of the *Standard solutions,* under the test for *Color of solution*, is added to comply with the Stage 6 Harmonization Draft. It is proposed to implement the revision via the *Fourth Interim Revision Announcement* pertaining to *USP 28–NF 23*, with an official date of Aug. 1, 2005.

(EMC: J. Lane) RTS—42152-2

Add the following:

■**Packaging and storage**—Preserve in tight containers. No specific storage requirements specified.■2S (*USP28*)

Change to read:

Color of solution—

Standard stock solutions—Prepare three solutions, *A, B,* and *C,* containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g per L):

A—2.4 : 0.6 : 0 : 7.0
B—2.4 : 1.0 : 0.4 : 6.2
C—9.6 : 0.2 : 0.2 : 0

•*Standard solutions*—[NOTE—Prepare the *Standard solutions* immediately before use.] Transfer 2.5 mL of *Standard stock solution A* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution A*. Transfer 2.5 mL of *Standard stock solution B* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution B*. Transfer 0.75 mL of *Standard stock solution C* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution C*.•4

Test solution—Use the *Test solution* prepared in the *Clarity of solution* test.

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 A, Standard solution B, Standard solution C,* and water to separate matching test tubes. Compare the *Test solution, Standard solution A, Standard solution B, Standard solution C,* and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* is not more intensely colored than *Standard solutions A, B, C* or water.

BRIEFING

Saccharin Calcium, *USP 28* page 1744 and page 1423 of *PF* 30(4) [July–Aug. 2004]. 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.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	–	+
Packaging and storage	+	–	+
Identification B	+	–	+
Identification C	–	–	+
Water	+	–	+
Readily carbonizable substances	+	–	+
Limit of benzoate and salicylate	–	–	+
Assay	+	–	+

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Heavy metals, Labeling, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification (IR).

Specific local attributes: USP: Organic volatile impurities.

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

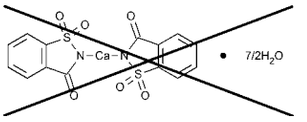
Differences between the **ADOPTION STAGE 6** document and the current *USP* monograph include the following:

(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 at room temperature are added.
(3) *USP Reference standards*—A reference for Saccharin Calcium is added for use in *Identification* test *A*.
(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, B,* and *D* are replaced with a more definitive IR absorption test. *Identification* test *C* is retained, but separated into two tests *(B* and *C).*
(7) *Water*—No change.
(8) *Readily carbonizable substances*—No change.
(9) *Selenium*—This test is deleted because it is unnecessary for this compound.
(10) *Limit of toluenesulfonamides*—The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method. The *Test solution* is corrected to that of the EP. Editorial changes are made.
(11) *Heavy metals*—No change.
(12) *Limit of benzoate and salicylate*—No change.
(13) *Organic volatile impurities*—No change.
(14) *Assay*—No change.

(EMC: J. Lane) RTS—42147-2

Change to read:

~~Saccharin Calcium~~



~~$C_{14}H_8CaN_2O_6S_2 \cdot 3\frac{1}{2}H_2O$ 467.49~~
~~1,2-Benzisothiazol-3(2*H*)-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 98.0 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.~~

~~**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 o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*~~

~~**Identification—**~~

~~**A:** Dissolve about 100 mg in 5 mL of sodium hydroxide solution (1 in 20), evaporate to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve in 20 mL of water, neutralize with 3 N hydrochloric acid, and filter: the addition of a drop of ferric chloride TS to the filtrate produces a violet color.~~

~~**B:** Mix 20 mg with 40 mg of resorcinol, add 10 drops of sulfuric acid, and heat the mixture in a suitable liquid bath at 200° for 3 minutes. Allow it to cool, and add 10 mL of water and an excess of 1 N sodium hydroxide: a fluorescent green liquid results.~~

~~**C:** A solution (1 in 10) meets the requirements of the tests for *Calcium* ⟨191⟩.~~

~~**D:** To 10 mL of a solution (1 in 10) add 1 mL of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate with cold water, and dry at 105° for 2 hours: it melts between 226° and 230°, the procedure for *Class I* being used (see *Melting Range or Temperature* ⟨741⟩).~~

~~**Water,** *Method I* ⟨921⟩: not more than 15.0%.~~

~~**Readily carbonizable substances** ⟨271⟩—Dissolve 200 mg in 5 mL of sulfuric acid TS, and maintain at a temperature of 48° to 50° for 10 minutes: the solution has no more color than *Matching Fluid A.*~~

~~**Selenium** ⟨291⟩: 0.003%.~~

~~**Toluenesulfonamides—**~~

~~*Internal standard solution, Standard stock solution,* and *Standard preparations*—Prepare as directed for *Internal standard solution, Standard stock solution,* and *Standard preparations* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph).~~

~~*Test preparation*—Prepare as directed under *Column Partition Chromatography* (see *Chromatography* ⟨621⟩), employing a chromatographic tube fitted with a porous glass disk in its base, a plastic stopcock on the delivery tube, and a reservoir on the top. Add a mixture consisting of 10 g of *Solid Support* and a solution of 2.0 g, accurately weighed, of Saccharin Calcium in 8.0 mL of sodium carbonate solution (1 in 20), and proceed as directed for *Test preparation* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph), beginning with "Pack the contents."~~

~~*Chromatographic system* and *Procedure*—Proceed as directed for *Chromatographic system* and *Procedure* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph).~~

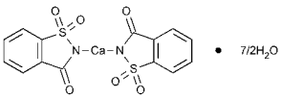
~~**Heavy metals,** *Method I* ⟨231⟩—Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid (1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the *Test Preparation:* the limit is 0.001%.~~

~~**Limit of 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**—Accurately weigh about 500 mg of Saccharin Calcium, and transfer completely to a separator with the aid of 10 mL of water. Add 2 mL of 3 N hydrochloric acid, and extract the precipitated saccharin first with 30 mL, then with five 20-mL portions, of a mixture of chloroform and alcohol (9 : 1). Evaporate the combined extracts on a steam bath to dryness, with the aid of a current of air, then dissolve the residue in 40 mL of alcohol, add 40 mL of water, mix, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination on a mixture of 40 mL of alcohol and 40 mL of water, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 20.22 mg of $C_{14}H_8CaN_2O_6S_2$.~~

▲Saccharin Calcium



$C_{14}H_8CaN_2O_6S_2 \cdot 3½H_2O$ 467.49

1,2-Benzisothiazol-3(2*H*)-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.~~ 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—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 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—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with the same solution 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 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—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 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 10 N sodium hydroxide.~~ Dissolve 10.0 g of the substance to be examined in about 45 mL of water. If necessary, adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 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~~ gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 µm). The injection port, column, and detector temperatures are maintained at 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 $C_{14}H_8CaN_2O_6S_2$·▲*USP29*

BRIEFING

Saccharin Sodium, *USP 28* page 1745 and page 1427 of *PF* 30(4) [July–Aug. 2004]. 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.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification B	+	+	+
Identification C	–	+	+
Acidity or alkalinity	+	+	+
Water	+	+	+
Readily carbonizable substances	+	+	+
Limit of benzoate and salicylate	–	+	+
Assay	+	+	+

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Packaging and storage, Heavy metals, Labeling, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification A (IR).

Specific local attributes: USP: Organic volatile impurities; JP: Description.

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

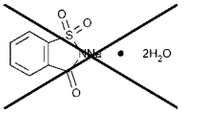
Differences between the **ADOPTION STAGE 6** document and the current *USP* monograph include the following:

(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 at room temperature are added.
(3) *Labeling*—No change.
(4) *USP Reference standards*—A reference for Saccharin Sodium 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* test *B* is replaced with a more definitive IR absorption test. *Identification* test *A* is retained, but separated into two 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. The *Test solution* is corrected to that of the EP. Editorial changes are made.
(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—42147-3

Change to read:

~~Saccharin Sodium~~



~~$C_7H_4NNaO_3S \cdot 2H_2O$ 241.20~~
~~1,2-Benzisothiazol-3(2*H*)-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*].~~

~~» Saccharin Sodium contains not less than 98.0 percent and not more than 101.0 percent of $C_7H_4NNaO_3S$, calculated on the anhydrous basis.~~

~~**Packaging and storage**—Preserve in well-closed containers.~~

~~**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 o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*~~

~~**Identification—**~~

~~**A:** The residue obtained by igniting it responds to the tests for *Sodium* ⟨191⟩.~~

~~**B:** To 10 mL of a solution (1 in 10) add 1 mL of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate with cold water until the last washing is free from chloride, and dry at 105° for 2 hours: it melts between 226° and 230°, the procedure for *Class I* being used (see *Melting Range or Temperature* ⟨741⟩).~~

~~**Alkalinity**—A solution (1 in 10) is neutral or alkaline to litmus, but no red color is produced with phenolphthalein TS.~~

~~**Toluenesulfonamides—**~~

~~*Internal standard solution, Standard stock solution,* and *Standard preparations*—Prepare as directed for *Internal standard solution, Standard stock solution,* and *Standard preparations* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph).~~

~~*Test preparation*—Prepare as directed under *Column Partition Chromatography* (see *Chromatography* ⟨621⟩), employing a chromatographic tube fitted with a porous glass disk in its base, a plastic stopcock on the delivery tube, and a reservoir on the top. Add a mixture consisting of 10 g of *Solid Support* and a solution of 2.0 g, accurately weighed, of Saccharin Sodium in 8.0 mL of sodium carbonate solution (1 in 20), and proceed as directed under *Test preparation* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph), beginning with "Pack the contents."~~

~~*Chromatographic system* and *Procedure*—Proceed as directed for *Chromatographic system* and *Procedure* in the test for *Toluenesulfonamide* under *Saccharin* (see *NF* monograph).~~

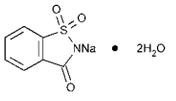
~~**Heavy metals,** *Method I* ⟨231⟩—Dissolve 4 g in 46 mL of water, add 4 mL of 1 N hydrochloric acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, and then filter through a dry filter, discarding the first 10 mL of the filtrate: the limit, determined on 25 mL of the subsequent filtrate, is 0.001%.~~

~~**Organic volatile impurities,** *Method IV* ⟨467⟩**:** meets the requirements.~~

~~**Other requirements**—It responds to *Identification* tests *A* and *B*, and meets the requirements of the tests for *Water, Benzoate and salicylate, Selenium,* and *Readily carbonizable substances* under *Saccharin Calcium*.~~

~~**Assay**—Proceed with Saccharin Sodium as directed in the *Assay* under *Saccharin Calcium*. Each mL of 0.1 N sodium hydroxide is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.~~

▲Saccharin Sodium



$C_7H_4NNaO_3S \cdot 2H_2O$ 241.20

1,2-Benzisothiazol-3(2*H*)-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*].

» 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.~~ 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 *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—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with ~~water~~ the same solution 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 the test for *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 the *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 10 N sodium hydroxide.~~ Dissolve 10.0 g of the substance to be examined in about 45 mL of water. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 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~~ gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 µm). The injection port, column, and detector temperatures are maintained at 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 $C_7H_4NNaO_3S$.▲*USP29*

MONOGRAPHS (NF)

BRIEFING

Saccharin, *NF 23* page 3070 and page 1450 of *PF* 30(4) [July–Aug. 2004]. 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 European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Packaging and storage	+	+	+
Loss on drying	+	+	+
Readily carbonizable substances	+	+	+
Residue on ignition	+	+	+
Limit of benzoate and salicylate	–	+	+
Assay	+	+	+

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Heavy metals, Melting range, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification (IR).

Specific local attributes: USP: Organic volatile impurities; JP: Description.

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

Differences between the **ADOPTION STAGE 6** document and the current *NF* monograph include the following:

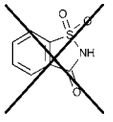
(1) In the opening paragraph (the Definition)—The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) *Packaging and storage*—Storage conditions at room temperature are added.
(3) *USP Reference standards*—A reference for Saccharin is added for use in the *Identification* 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. Editorial corrections are made.
(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—42147-1

Change to read:

~~Saccharin~~



~~$C_7H_5NO_3S$ 183.19~~
~~1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide.~~
~~1,2-Benzisothiazolin-3-one-1,1-dioxide [*81-07-2*].~~

~~» Saccharin contains not less than 98.0 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.~~

~~**USP Reference standards** ⟨11⟩—*USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*~~

~~**Identification—**~~

~~**A:**—Dissolve about 100 mg in 5 mL of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve it in 20 mL of water, neutralize the solution with 3 N hydrochloric acid, and filter: the addition of a drop of ferric chloride TS to the filtrate produces a violet color.~~

~~**B:**—Mix 20 mg with 40 mg of resorcinol, add 10 drops of sulfuric acid, and heat the mixture in a suitable liquid bath at 200° for 3 minutes. Allow it to cool, and add 10 mL of water and an excess of 1 N sodium hydroxide: a fluorescent green liquid results.~~

~~**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 TS, and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than *Matching Fluid A.*~~

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

~~**Toluenesulfonamides—**~~

~~*Internal standard solution*—Place 10 mg of *n*-tricosane in a 10-mL volumetric flask, dissolve in *n*-heptane, dilute with *n*-heptane to volume, and mix.~~

~~*Standard stock solution*—Transfer 20 mg each, accurately weighed, of USP *o*-Toluenesulfonamide RS and of USP *p*-Toluenesulfonamide RS to a 10-mL volumetric flask, dissolve in methylene chloride, dilute with methylene chloride to volume, and mix.~~

~~*Standard preparations*—Transfer 100, 150, 200, and 250 µL, respectively, of *Standard stock solution* to each of four 10-mL volumetric flasks. Add 250 µL, accurately measured, of *Internal standard solution* to each flask, dilute each with methylene chloride to volume, and mix. These preparations contain, in each mL, 25 µg of *n*-tricosane and, respectively, 20, 30, 40, and 50 µg of each toluenesulfonamide isomer.~~

~~*Test preparation*—Prepare as directed under *Column Partition Chromatography* (see *Chromatography* ⟨621⟩), employing a chromatographic tube fitted with a porous glass disk in its base, a plastic stopcock on the delivery tube, and a reservoir at the top. Add a mixture consisting of 12 g of *Solid Support* and a solution of 2.0 g, accurately weighed, of Saccharin with 12 mL of filtered sodium bicarbonate solution (1 in 11). Add about 200 mg of sodium bicarbonate to effect complete solution of the saccharin. Pack the contents of the tube by tapping the column on a padded surface, and then by tamping firmly from the top. Place 100 mL of methylene chloride in the reservoir, and adjust the stopcock so that 50 mL of eluate is collected in 20 to 30 minutes. To the eluate add 25 µL of *Internal standard solution*, mix, and concentrate the solution, by suitable means, to a volume of 1.0 mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—Under typical conditions, the instrument is equipped with a flame ionization detector, and contains a 1.8-m × 3.2-mm glass column packed with 10% liquid phase G3 on 100- to 120-mesh support S1AB, utilizing a glass-lined sample introduction system or on-column injection. The injector port, column, and detector block are maintained at temperatures of about 225°, 210°, and 250°, respectively, and dry helium is used as the carrier gas at a flow rate of about 30 mL per minute.~~

~~*Procedure*—Inject portions (about 2.5 µL) of the *Standard preparations*, successively, into a gas chromatograph, and record each chromatogram so as to obtain at least 50% of maximum recorder response. Measure the areas under the first (*o*-toluenesulfonamide), second (*p*-toluenesulfonamide), and third (*n*-tricosane) peaks, and for each chromatogram record the values as A_o, A_p, and A_n, respectively. Calculate the ratios R_o and R_p taken by the equations:~~

$$R_o = A_o / A_n \text{ and } R_p = A_p / A_n,$$

~~and prepare standard curves by plotting the concentrations, in µg per mL, of USP *o*-Toluenesulfonamide RS and of USP *p*-Toluenesulfonamide RS in the *Standard preparations* versus R_o and R_p, respectively. [NOTE—Relative retention times are, approximately, 0.39 for *o*-toluenesulfonamide, 0.46 for *p*-toluenesulfonamide, and 1.0 for *n*-tricosane.] Similarly inject a portion (about 2.5 µL) of the *Test preparation*, and record the chromatogram. Measure the areas under the first (*o*-toluenesulfonamide), second (*p*-toluenesulfonamide), and third (*n*-tricosane) peaks, and record the values as a_o, a_p, and a_n, respectively. Calculate the ratios r_o and r_p taken by the equations:~~

$$r_o = a_o / a_n \text{ and } r_p = a_p / a_n,$$

~~and, from the standard curve, determine the concentration, in µg per mL, of each toluenesulfonamide isomer in the *Test preparation:* the total amount of toluenesulfonamides in the specimen taken is not more than 0.0025%.~~

~~**Selenium** ⟨291⟩: 0.003%, a 100-mg specimen, mixed with 100 mg of magnesium oxide, being used.~~

~~**Heavy metals,** *Method II* ⟨231⟩: 0.001%.~~

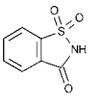
~~**Benzoic and salicylic acids**—To 10 mL of a hot, saturated solution of it add ferric chloride TS, dropwise: no precipitate or violet color appears in the liquid.~~

~~**Organic volatile impurities,** *Method V* ⟨467⟩**:** meets the requirements.~~

~~*Solvent*—Use dimethyl sulfoxide.~~

~~**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 VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 18.32 mg of $C_7H_5NO_3S$.~~

▲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.~~ 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 *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—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with the same solution 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 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—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 the *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 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 10 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 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~~ gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 µm). The injection port, column, and detector temperatures are maintained at 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.

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 $C_7H_5NO_3S$.▲*NF24*

Harmonization

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.*

Pharmacopeial Forum
Vol. 31(2) [Mar.–Apr. 2005]

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.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention, Inc., (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

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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Common Pharmacopeial Calculations in USP Monographs

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ABSTRACT This article was prompted by questions USP has received pertaining to the formulas used in official monographs. It attempts to explain most commonly used formulas by citing representative examples and analyzes all factors that have led to the final formula. In many cases, factors such as dilution and/or relative response factors are combined in a single numerical value. It is not always obvious how the numerical factor was derived until a thorough analysis is completed. Examples were chosen from three areas: miscellaneous tests such as *Loss on drying* and *Loss on ignition,* assays comprising various procedures, and related compounds determined by HPLC. Recommendations to simplify the format and express the formulas in a more explanatory manner are included.

INTRODUCTION

Calculations are part of almost every monograph procedure. Monograph procedures use various techniques, experimental designs, and corresponding formulas to calculate results. In order to understand the results of a test, the analyst should have complete comprehension of the interdependence of the formula and the experimental design.

The purpose of this *Stimuli* article is to present detailed explanations of many of the most commonly used pharmacopeial calculations. Three categories of formulas are included: Calculations for tests such as *Loss on drying* and *Loss on ignition* are included under miscellaneous tests; the *Assay* section includes formulas for titrimetric and spectroscopic procedures; and the related compounds and assay categories include formulas used in quantitative chromatographic [high-performance liquid chromatography (HPLC) and gas chromatography (GC)] procedures. As applicable, formulas from USP drug substance and drug product monographs are used to illustrate various examples. Although many examples are presented, this article is not meant to be an exhaustive review of every possible type of compendial formula. For the purposes of this article, calculations for biological tests are not included.

The result of this review of pharmacopeial calculations is a list of recommendations for presenting formulas in monograph procedures. This list is offered to the pharmaceutical industry and to USP as a tool for drafting monograph formulas so that they are scientifically sound and useful to the analyst.

The authors have made a few assumptions in writing this article. First, the analyst must have the required theoretical knowledge and practical laboratory training in order to perform the monograph procedure. Second, a thorough understanding of the *USP General Notices* and applicable General Chapters is critical in order to execute the procedures correctly. Finally, the analyst also should have working knowledge of the appropriate regulatory guidances and International Conference on Harmonization (ICH) guidelines and the USP "Guideline for Submitting Requests for Revision to *USP–NF*" (*1*).

MISCELLANEOUS CALCULATIONS

Following are sample calculations for tests such as *Loss on drying* (LOD) or *Loss on ignition* (LOI) needed for the correction of the assay result when appropriate.

Percent LOD

This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified (*2*). In this simple technique, the sample is weighed, then heated, and the dried sample is reweighed. The difference in the sample weight is the volatile content. A typical calculation is as follows:

Weight of container = C

Weight of container and test sample before drying = T

Weight of container and test sample after final drying = F

$$\%LOD = [(T - F)/(T - C)] \times 100$$

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Percent LOI

This procedure determines the percentage of test material that is volatilized and driven off under the conditions specified (*3*). The sample is initially weighed and then ignited in a suitable oven. The sample is cooled in a desiccator and accurately reweighed. The percentage loss for the test material is calculated as follows:

Weight of container = C

Weight of container and test sample before ignition = T

Weight of container and test sample after final ignition = F

$$\%LOI = [(T - F)/(T - C)] \times 100$$

ASSAY

Assay procedures determine the content of an active ingredient in a drug substance or a drug product. The acceptance criteria for an assay are indicated in the definition section of the *USP* monograph and generally are expressed as a percent. However, the value calculated in the assay generally is the quantity (e.g., mg or µg). Therefore, further calculations may be needed to convert the assay result to the appropriate unit (usually percent) consistent with the Definition section of the monograph.

Example 1 (Assay "As Is")

Malathion contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{19}O_6PS_2$.
The quantity of Malathion obtained in the assay = Q
The quantity of Malathion taken = T

Assume:
Q = 495 mg
T = 500.0 mg

Calculation: $Q/T \times 100 = 495/500.0 \times 100 = 99.0$ percent.

The percent acceptance criteria in the definition for the article without further qualification generally indicate the assay result "as is." However, the acceptance criteria for the assay frequently indicate limits to be calculated on the anhydrous basis, on the dried basis, or on the ignited basis.

The following section from the *USP General Notices* (p. 7) may help analysts understand the common calculations involving appropriate correction factors:

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.

Example 2 (Assay Result Corrected for Loss on Drying)

Miconazole contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{14}C_{l4}N_2O$, calculated on the dried basis.
Quantity of $C_{18}H_{14}C_{l4}N_2O$ obtained in the assay = Q
Quantity of Miconazole taken = T
Percent LOD = A

Assume:
Q = 295.0 mg
T = 300.0 mg
A = 0.34%

Assay result = $[Q/T/(100 - A)/100] \times 100 = [295.0/300.0/(100 - 0.34)/100] \times 100 = 98.7$ percent.

Example 3 (Assay Result Corrected for Water)

Acyclovir contains not less than 98.0 percent and not more than 101.0 percent of $C_8H_{11}N_5O_3$, calculated on the anhydrous basis.
Quantity of $C_8H_{11}N_5O_3$ obtained in the assay = Q
Quantity of Acyclovir taken = T
Percent of water = A

Assume:
Q = 96.0 mg
T = 99.8 mg
A = 3.54 %

Assay result = $[Q/T/(100 - A)/100] \times 100 = [96.0/99.8/(100 - 3.54)/100] \times 100 = 99.7$ percent

Example 4 (Assay Result Corrected for Loss on Ignition)

Ferric Oxide contains not less than 97.0 percent and not more than 100.5 percent of Fe_2O_3, calculated on the ignited basis.
Quantity of Fe_2O_3 obtained in the assay = Q
Quantity of Ferric Oxide taken = T
Percent LOI = A

Assume:
Q = 2.48 mg
T = 2.52 mg
A = 1.24%

Assay result = $[Q/T/(100 - A)/100] \times 100$ = [2.48/2.52/ (100 – 1.24/100)] × 100 = 99.6 percent

The *USP General Notices* also state (p. 7):

> 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).

Example 5 (Assay Result on Previously Dried Sample)

> Ganciclovir contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_{13}N_5O_4$, calculated on the previously dried basis.
> Quantity of $C_9H_{13}N_5O_4$ obtained in the assay = Q
> Quantity of Ganciclovir, previously dried, taken = T
>
> Assume:
> Q = 10.7 mg
> T = 10.5 mg
>
> Assay result = $Q/T \times 100$ = 10.7/10.5 × 100 = 101.9 percent.

Example 6: (Assay Result on Previously Dried Sample)

In some cases, the procedure in the monograph will indicate that the sample should be dried before use.

> Adenosine contains not less than 99.0 percent and not more than 101.0 percent of $C_{10}H_{13}N_5O_4$ calculated on the dried basis.
> *Assay*—Dissolve about 200 mg of Adenosine, previously dried at 105° for 2 hours and 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 correction. Each mL of 0.1 N perchloric acid is equivalent to 26.72 mg of $C_{10}H_{13}N_5O_4$.

In the two previous cases, the test sample must be dried first and then assayed. There is no actual additional calculation for the dried basis. Rather, the term "calculated on the dried basis" or "calculated on the previously dried basis" implies that the values calculated for the assay have already been corrected for the volatile compounds (water and/or solvents) because the test sample was previously dried.

The acceptance criteria for the assay also can be expressed on the solvent-free basis or other variations and combination terms. In this case, the assay result needs to be corrected for the solvent, if present. A test for specific residual solvent(s) or a general test for volatile organic impurities is usually provided in the monograph.

Example 7 (Assay Result Corrected for Both Water and Solvent)

> Lamivudine contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_{11}N_3O_3S$, calculated on the anhydrous and solvent-free basis.
> Quantity of $C_8H_{11}N_3O_3S$ in the portion of Lamivudine obtained in the assay = Q
> Quantity of Lamivudine taken = T
> Percent of water = A
> Percent of residual solvent = B
>
> Assume:
> Q = 26.0 mg
> T = 25.9 mg
> A = 0.183%
> B = 0.281%
>
> Assay result = $[Q/T/(100 - A - B)/100] \times 100$ =
>
> [26.0/25.9/ (100 – 0.183 – 0.281)/100] × 100 = 100.9 percent.
>
> NOTE—When the assay result in a *USP* monograph is corrected for LOD, LOI, water, residual solvent, or combinations of such factors, not only must the acceptance criteria for the assay be met but all other acceptance criteria for the monograph also have to be achieved. In other words, the assay value of 100.9% obtained above is within the tolerance value of 98.0% to 102.0%. In addition, both water and residual solvent must remain within the acceptance criteria of not more than 0.2% and 0.3%, respectively, for Lamivudine.

COMMON CALCULATIONS FOR DETERMINATION OF THE ASSAY RESULT

In this section, common or typical calculations used for the determination of assay results are discussed. Simple and more complex calculations for both drug substance and dosage forms will be presented. Because most of the assay procedures are based on chromatography, titration, or spectroscopy, examples using such techniques will be explored. However, a detailed discussion of the different types of techniques used is beyond the scope of this *Stimuli* article. It is assumed that the reader has a basic understanding of the concepts and the principles of chromatographic, titration, and spectroscopic procedures. As necessary, the reader

is advised to consult USP General Chapters *Chromatography* ⟨621⟩ (*4*), *Titrimetry* ⟨541⟩ (*5*), *Spectrophotometry and Light-Scattering* ⟨851⟩ (*6*), and books on analytical chemistry and quantitative analysis (e.g., *7* and *8*).

In the following examples, only the relevant portions of the monograph as related to the assay and the corresponding calculations are selected. Please refer to the current *USP–NF* to review the complete monographs and/or procedures.

Chromatography

Example 1 (HPLC)

Isoniazid contains not less than 98.0 percent and not more than 102.0 percent of $C_6H_7N_3O$, calculated on the dried basis.

Assay preparation—Transfer about 16 mg of Isoniazid, accurately weighed, to a 50-mL volumetric flask, dissolve in *Mobile phase,* dilute with *Mobile phase* to volume, and mix. Calculate the quantity, in mg, of $C_6H_7N_3O$ in the portion of Isoniazid taken by the formula:

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

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

The simple calculation given above is very common in *USP* monographs. The quantitation is based on an external Reference Standard. In addition, a factor is also introduced to correct for the volume dilution. To further clarify the equation using the appropriate unit factors:

The quantity, in mg, of $C_6H_7N_3O$ in the portion of Isoniazid taken = 50 (mL) C (mg/mL) [r_U (area of the major peak in assay preparation)/r_S (area of the major peak in the reference standard preparation)].

Example 2 (HPLC)

Benzoyl Peroxide Gel is benzoyl peroxide in a suitable gel base. It contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of benzoyl peroxide ($C_{14}H_{10}O_4$).

Assay preparation—Transfer an accurately weighed quantity of Gel, equivalent to about 40 mg of benzoyl peroxide, to a 50-mL volumetric flask. Add 40 mL of acetonitrile, and shake until the material is thoroughly dispersed. Sonicate the mixture for 5 minutes, dilute with acetonitrile to volume, mix, and filter. Pipet 10 mL of the filtrate and 5 mL of *Internal standard solution* into a 25-mL volumetric flask, dilute with acetonitrile to volume, and mix. Calculate the quantity, in mg, of benzoyl peroxide ($C_{14}H_{10}O_4$) in the portion of Gel taken by the formula:

$$125C(R_U / R_S),$$

in which C is the concentration, in mg per mL, of benzoyl peroxide in the *Standard preparation,* and R_U and R_S are the peak response ratios of benzoyl peroxide to ethyl benzoate obtained from the *Assay preparation* and the *Standard preparation,* respectively.

This formula has the same general concept and can be simplified as:

$$DC(R_U / R_S),$$

D = Dilution factor = 50 (mL) × 25 (mL)/10 (mL) = 125.

Example 3 (HPLC)

Atovaquone Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of atovaquone ($C_{22}H_{19}C_lO_3$).

Assay preparation—Transfer approximately 5.2 g of the well-mixed Oral Suspension, accurately weighed, to a low-actinic 250-mL volumetric flask. Add 50 mL of water, swirl for about 5 minutes, add 150 mL of 0.1 M methanolic sodium hydroxide, and sonicate for about 15 minutes. Allow to cool, dilute with 0.1 M methanolic sodium hydroxide to volume, and mix. Immediately filter a 20-mL portion, discarding the first 5 mL of the filtrate. Transfer 3.0 mL of the clear filtrate to a low-actinic 100-mL volumetric flask, dilute with a mixture of methanol and water (1:1) to volume, and mix. Calculate the quantity, in mg, of atovaquone ($C_{22}H_{19}C_lO_3$) in each mL of the Oral Suspension taken by the formula:

$$(25{,}000/3)(C/V)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Atovaquone 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 atovaquone peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

This formula has the same general concept and can be simplified as:

$$DC(r_U / r_S),$$

D = Dilution factor = 250 (mL) × 100 (mL)/3 (mL) = 25,000/3.

NOTE—In the example above, *V* is defined as "the volume, in mL, of Oral Suspension taken to prepare the *Assay preparation.*" However, the weight rather than the volume of Oral Suspension was taken to prepare the *Assay preparation*. In other words, the weight, approximately 5.2 grams in this case, has to be converted to volume using the density of the Oral Suspension, 1.04 g per mL as given in the related compound section of the monograph. The reason for taking the weight rather than the volume is the difficulty of accurately measuring the volume of the Oral Suspension directly.

In several *USP* monographs, the assay calculations are corrected for the molecular weight ratio. This is usually done when the RS used and the content determined are in two different forms (e.g., salt and free base). Therefore, a correction factor (the molecular weight ratio) is included in the equation.

Example 4 (HPLC)

Dobutamine Injection is a sterile solution of Dobutamine Hydrochloride in Water for Injection. It contains an amount of Dobutamine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dobutamine ($C_{18}H_{23}NO_3$).
Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 25 mg of dobutamine, to a 50-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix. Calculate the quantity, in mg, of $C_{18}H_{23}NO_3$ in the portion of Injection taken by the formula:

$$(301.39/337.84)(50C)(r_U/r_S),$$

in which 301.39 is the molecular weight of dobutamine (free base), 337.84 is the molecular weight of dobutamine hydrochloride; *C* is the concentration, in mg per mL, of USP Dobutamine 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.

NOTE—The RS used is dobutamine hydrochloride (salt), but the definition is expressed in terms of percentage of the labeled amount of dobutamine (free base). Therefore, the correction factor (the molecular weight ratio) is included in the equation to calculate the dobutamine content.

Example 5 (GC)

Hyoscyamine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{23}NO_3$.
Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 0.86 mg of hyoscyamine, to a separator containing 5 mL of *pH 9.0 buffer,* and add, by pipet, 2.0 mL of *Internal standard solution*. Proceed as directed under *Standard preparation,* beginning with "adjust with 1 N sodium hydroxide to a pH of 9.0."
Standard preparation—Dissolve about 10 mg of USP Hyoscyamine Sulfate RS, accurately weighed, in water contained in a 100-mL volumetric flask, add water to volume, and mix. Prepare fresh daily. Pipet 10.0 mL of this solution into a separator, add 2.0 mL of *Internal standard solution* and 5.0 mL of *pH 9.0 buffer,* and adjust with 1 N sodium hydroxide to a pH of 9.0. Extract with two 10-mL portions of methylene chloride, filter the methylene chloride extracts through 1 g of anhydrous sodium sulfate supported by a small cotton plug in a funnel into a 50-mL beaker, and evaporate under nitrogen to dryness. Dissolve the residue in 2.0 mL of methylene chloride.
Procedure—Inject 1-µL portions of the *Assay preparation* and the *Standard preparation* successively into the gas chromatograph . . . Calculate the ratio, A_U, of the area of the hyoscyamine peak to the area of the internal standard peak in the chromatogram from the *Assay preparation,* and similarly calculate the ratio, A_S, in the chromatogram from the *Standard preparation*. Calculate the quantity, in mg, of $C_{17}H_{23}NO_3$ in the portion of tablets taken by the formula:

$$(289.37/676.83)(W/10)(A_U/A_S),$$

in which 289.37 and 676.83 are the molecular weights of hyoscyamine and anhydrous hyoscyamine sulfate, respectively; and *W* is the weight, in mg, of USP Hyoscyamine Sulfate RS taken for the *Standard preparation*.

NOTE—Only 10.0 mL of 100 mL standard solution was used. Therefore, the correction factor 10 (10/100) is used in the denominator.

Titration

USP monographs do not provide chemical equations of reactions used for assay calculations. However, they provide directions for calculating the assay result. We provide a general guideline for such calculations.

Direct titration is the treatment of a soluble substance, contained in solution in a suitable vessel (the titrate), with an appropriate standardized solution (the titrant), the endpoint being determined instrumentally or visually with the aid of a suitable indicator.

Example 1 (Direct Titration)

Ketoprofen contains not less than 98.5 percent and not more than 101.0 percent of $C_{16}H_{14}O_3$, calculated on the dried basis.
Assay—Dissolve about 200 mg of Ketoprofen, accurately weighed, in 25 mL of alcohol. Add 25 mL of water and several drops of phenol red TS, and titrate with 0.1 N sodium hydroxide having been standardized by a similar titration of primary standard benzoic acid. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

$$\%\text{Assay: } [(V - B) \times N \times F \times 100] / [TN \times W \times (100 - A)/100]$$

V: Sample titrant volume (mL)
B: Blank titrant volume (mL)
N: Titrant normality
F: Equivalence Factor (mg sample/mL of TN)
TN: Theoretical normality
W: Sample weight (mg)
A: Assay correction for LOD

Assume:
$V = 8.5$ mL
$B = 1.4$ mL
$N = 0.11$
$TN = 0.1$
$W = 202$ mg
$A = 0.42\%$

$$\text{Assay result} = [(V - B) \times N \times F \times 100] / [TN \times W \times (100 - A)/100] =$$

$$[(8.5–1.4) \times 0.11 \times 25.43 \times 100]/ [0.1 \times 202 \times (100 – 0.42)/100] = 98.7\%$$

Some pharmacopeial assays require the addition of a measured volume of a volumetric solution in excess of the volume actually needed to react with the substance being assayed. The excess of this solution is then titrated with a second volumetric solution in a direct titration. This constitutes a residual titration and is also known as back titration. The quantity of the substance being titrated is calculated from the difference between the volume of the volumetric solution originally added, corrected by blank, and that consumed by the titrant in the back titration (*5*).

Example 2 (Residual Titration or Back Titration)

Methenamine, dried over phosphorus pentoxide for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_6H_{12}N_4$.
Assay—Transfer about 1 g of Methenamine, previously dried and accurately weighed, to a beaker. Add 40.0 mL of 1 N sulfuric acid VS, and heat to a gentle boil, adding water from time to time if necessary, until the formaldehyde has been expelled. Test for the absence of formaldehyde by adding a drop of the assay solution to a glass fiber filter disk, on a watch glass, on which has previously been placed 3 or 4 drops of *Chromotropic acid spot test solution*. Formaldehyde produces a violet color with this reagent; repeat the test until no violet color is obtained on the warmed test filter disk upon comparison with a blank filter disk to which no assay specimen is added. Cool, add 20 mL of water, then add methyl red TS, and titrate the excess acid with 1 N sodium hydroxide VS. Perform a blank determination. Each mL of 1 N sulfuric acid is equivalent to 35.05 mg of $C_6H_{12}N_4$.

$$\%\text{Assay: } [(B - V) \times N \times F \times 100] / [TN \times W]$$

B: Titrant volume (mL) for blank titration
V: Titrant volume (mL) for titration of sample
N: Titrant normality
F: Equivalence Factor = (mg sample/mL of TN)
TN: Theoretical normality
W: Sample weight (mg)

Assume:
$B = 43.78$ mL
$V = 15.10$ mL
$F = 35.05$ mg/mL (given)
$N = 0.9993$
$TN = 1$
$W = 1007.8$ mg (previously dried)

$$\text{Assay result} = (43.78 \text{ mL} - 15.10 \text{ mL}) \times 0.9993 \times 35.05 \text{ mg/mL} \times 100/(1 \times 1007.8 \text{ mg}) = 99.7\%$$

Determination of Equivalence Factor in Titration-Based Assays

The titrimetric method is based on a general chemical reaction as below:

$$\alpha A + \beta R \rightarrow \text{Products}$$

where α molecules of an analyte (e.g., titrate), A, reacts with β molecules of reactant (e.g., titrant), R.

Stoichiometric calculations can be made using either moles (molecular weight) or equivalent (equivalent weight).

The equivalent weight (*EW*) and molecular weight (*MW*) are related by the following equation:

$$EW = MW/n,$$

where *n* is the number of electrons transferred in the reaction. Thus the value of *n* depends on the reaction. In any titration reaction, the same number of equivalents of titrate and titrant react at the endpoint.

For example, for simple acid–base reactions:

$H^+ + OH^- \rightarrow H_2O$; $n = 1$
$CO_3^{2-} + 2\ H^+ \rightarrow [H_2CO_3] \rightarrow H_2O + CO_2$, $n = 2$
$CO_3^{2-} + H^+ \rightarrow HCO_3^-$, $n = 1$

And the following are examples of redox reactions:

$MnO_4^- + 8\ H^+ + 5\ e \rightarrow Mn^{2+} + 4\ H_2O$; $n = 5$
$H_2O_2 \rightarrow O_2 + 2\ H^+ + 2\ e$; $n = 2$
$Cr_2O_7^{2-} + 14\ H^+ + 6\ e \rightarrow 2\ Cr3^+ + 7\ H_2O$; $n = 6$

Example 3 (Acid-Base Titration)

Sodium Bicarbonate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $NaHCO_3$.

Assay—Weigh and finely powder not fewer than 20 Tablets. Weigh accurately a portion of the powder, equivalent to about 2 g of sodium bicarbonate, dissolve in 100 mL of water, add methyl red TS, and titrate with 1 N hydrochloric acid VS. Add the acid slowly, with constant stirring, until the solution becomes faintly pink. Heat the solution to boiling, cool, and continue the titration until the pink color no longer fades after boiling. Each mL of 1 N hydrochloric acid is equivalent to 84.01 mg of $NaHCO_3$.

$$NaHCO_3 + HCl \rightarrow NaCl + CO_2 + H_2O$$

Number of equivalents HCl = Number of equivalents $NaHCO_3$

$V \times N$ = Number of equivalents $NaHCO_3$ (NOTE—*V* is in liters)

1 mL of 1 N HCl = mequivalents $NaHCO_3$ = MW/n = 84.01 mg/1 = 84.01 mg

Example 4 (Redox Titration)

Hydrogen Peroxide Concentrate contains not less than 29.0 percent and not more than 32.0 percent, by weight, of H_2O_2.

Procedure: Weigh accurately about 1 mL of Concentrate in a tared 100-mL volumetric flask, dilute with water to volume, and mix. To 20.0 mL of this solution add 20 mL of 2 N sulfuric acid, and titrate with 0.1 N potassium permanganate VS. Each mL of 0.1 N potassium permanganate is equivalent to 1.701 mg of H_2O_2.

Reactions:

$$MnO_4^- + 8H^+ + 5e \rightarrow Mn^{2+} + 4H_2O \qquad (1)$$

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e \qquad (2)$$

Multiply equation (1) by 2, equation (2) by 5 and add:

$2\ MnO_4^- + 6\ H^+ + 5\ H_2O_2 \rightarrow$
$2\ Mn^{2+} + 8\ H_2O + 5\ O_2$
or
$2\ KMnO_4 + 3\ H_2SO_4 + 5\ H_2O_2 \rightarrow$
$2\ MnSO_4 + 8\ H_2O + 5\ O_2 + K_2SO_4$

Number of equivalents $KMnO_4$ = Number of equivalents H_2O_2

$V_1 \times N_1$ = Number of equivalents H_2O_2
(*V* is in liters)

NOTE—Equivalent weight (*EW*) = Molecular weight (*MW*)/*n*

n = 2 for H_2O_2 because this is the number of electrons transferred from H_2O_2 in reaction 2 above.

1 mL of 1 N $KMnO_4$ = 34.01/2 mg H_2O_2 = 17.01 mg H_2O_2.

But the titration uses 0.1 N $KMnO_4$. Thus, 1 mL of 0.1 N $KMnO_4$ = 1.701 mg of H_2O_2.

Spectroscopy and Other Methods

USP contains numerous examples of analytical techniques used in the *Assay* section other than chromatography or titrimetry. In the simplest cases, the measurement of a signal is directly proportional to the amount of the material taken, and the formula contains only the dilution and response factors.

Example 1 (Acetazolamide—Assay Using IR)

Acetazolamide contains not less than 98.0 percent and not more than 102.0 percent of $C_4H_6N_4O_3S_2$, calculated on the anhydrous basis.

Assay—Dissolve about 200 mg of Acetazolamide, accurately weighed, in a small volume of pyridine in a 10-mL volumetric flask, add the solvent to volume, and

mix. Similarly, dissolve an accurately weighed quantity of USP Acetazolamide RS in pyridine to obtain a *Standard solution* having a known concentration of about 20 mg per mL. Concomitantly determine the absorbances of both solutions in 0.1-mm cells at the wavelength of maximum absorbance at about 7.38 µm (1350 cm^{-1}), with a suitable IR spectrophotometer, using pyridine as the blank. Calculate the quantity, in mg, of $C_4H_6N_4O_3S_2$ in the portion of Acetazolamide taken by the formula:

$$10C(A_U/A_S),$$

in which C is the concentration, in mg per mL, of USP Acetazolamide RS in the *Standard solution,* and A_U and A_S are the absorbances of the solution of Acetazolamide and the *Standard solution,* respectively.

In this example IR absorbance, A_U, at specified wavelength is compared to that of the reference standard, A_S. Both values are proportional to the concentration. The quantity, in mg, of the $C_4H_6N_4O_3S_2$ in the portion of Acetazolamide taken = 10 (mL) C (mg/mL) (A_U/A_S).

Example 2 (Assay Using UV)

Nalorphine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{19}H_{21}NO_3 \cdot HCl$, calculated on the dried basis.
Assay—Transfer about 25 mg of Nalorphine Hydrochloride, accurately weighed, to a 250-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Concomitantly determine the absorbances of this solution and of a *Standard solution* of USP Nalorphine Hydrochloride RS in the same medium having a known concentration of about 100 µg per mL in 1-cm cells at the wavelength of maximum absorbance at about 285 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_{19}H_{21}NO_3 \cdot HCl$ in the Nalorphine Hydrochloride taken by the formula:

$$0.25C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Nalorphine Hydrochloride RS in the *Standard solution,* and A_U and A_S are the absorbances of the solution of Nalorphine Hydrochloride and the *Standard solution,* respectively.
NOTE—The factor 0.25 is derived by combination of the dilution factor (250 mL) and unit conversion (µg to mg).
250 (mL) × C (µg/mL) × 1 mg/1000 µg = 0.25

Example 3 (Cefamandole Nafate—Assay Using Polarography)

Cefamandole Nafate has a potency equivalent to not less than 810 µg and not more than 1000 µg of cefamandole ($C_{18}H_{18}N_6O_5S_2$) per mg, calculated on the anhydrous basis.
Standard preparation—Transfer about 12 mg of USP Cefamandole Nafate RS, accurately weighed, to a 50-mL volumetric flask containing 4 mL of water. Immediately before use, add 30.0 mL of *pH 2.3 buffer,* dilute with water to volume, and mix.
Assay preparation—Using Cefamandole Nafate, prepare as directed under *Standard preparation*.
Procedure—Transfer a portion of the *Assay preparation* to a suitable polarographic cell. Deaerate by bubbling scrubbed nitrogen through the solution for 5 minutes, and redirect the nitrogen flow to the surface outlet. Insert the dropping mercury electrode of a suitable polarograph (*9*) capable of measuring a current of 0.5 microampere or appropriate current to maintain on-scale response, using an average capillary, and a drop rate of 1 per second. Record the polarogram in the differential pulse mode from –0.3 volts to –1.05 volts, using a saturated calomel reference electrode and platinum wire counter electrode. Determine the peak height obtained, in microamperes, where the peak height is defined as the perpendicular distance from the extrapolated baseline to the highest point of the peak as compared to the full-scale current range. Similarly, determine the peak current of the *Standard preparation*. Calculate the quantity, in µg, of $C_{18}H_{18}N_6O_5S_2$ in each mg of the Cefamandole Nafate taken by the formula:

$$P(W_S/W_U)(i_U/i_S),$$

in which P is the potency, in µg of cefamandole per mg, of USP Cefamandole Nafate RS, W_S and W_U are the quantities, in mg, of USP Cefamandole Nafate RS and Cefamandole Nafate taken to prepare the *Standard preparation* and the *Assay preparation,* respectively, and i_U and i_S are the peak currents, in microamperes, from the *Assay preparation* and the *Standard preparation,* respectively.

This direct comparison is corrected by the potency factor, in µg per mg, according to the labeled value for the reference standard, and the result is expressed in the same units.

RELATED COMPOUNDS

A primary goal of the USP is to provide public standards that ensure the purity, strength, and quality of official articles. One mechanism for assessing the purity of an article is the detection and quantitation of related compounds. To this end, monographs may include a *Related compounds* or *Chromatographic purity* test. Chromatographic procedures are commonly accepted means by which impurities can be separated and quantitated. For this reason, chromatographic procedures, particularly high-performance liquid chromatography (HPLC), are widely used in the pharmaceutical industry and in USP monographs.

According to ICH guideline Q3A(R), *Impurities in New Drug Substances,* there are three classes of impurities: inorganic impurities, residual solvents, and organic impurities. Inorganic impurities include catalysts, ligands, heavy metals, and metal salts. Though it is important to identify and quantitate these types of impurities, analysis and quantitation typically are not accomplished using chromatographic procedures. Residual solvents, solvents remaining from the synthesis and/or purification processes, or formed during formulation are generally measured via gas chromatography (GC). Detection and quantitation of residual solvents are addressed in *USP* General Chapter *Organic Volatile Impurities* ⟨467⟩ (*10*).

Types of organic impurities include starting materials, process intermediates, degradants, or reagents. This section includes an exploration of formulas used in USP monographs to calculate the levels of organic impurities. *USP* monographs include chromatographic procedures for the quantitation of impurities (specified, unspecified, identified, and unidentified). If an impurity is characterized, it is known as a specified impurity. The chemical identity of a specified impurity may be known or unknown, i.e., identified or unidentified. For monograph purposes, the impurity may be identified by its official USP reference standard name or chemical name, by a relative retention time designation, or by a descriptor such as Impurity 1 or Impurity A.

USP monographs describe procedures for quantitation of organic impurities or degradants as *Chromatographic purity* or *Related compounds* test; this name generally refers to a quantitative separation technique such HPLC or GC. Results for *Chromatographic purity* or *Related compounds* typically are expressed in percent, the most commonly used units for the acceptance criteria. Acceptance criteria should be provided for each specified identified impurity, each specified unidentified impurity, any unspecified impurity with acceptance criteria of not more than the identification threshold, and total impurities in compliance with ICH Q3A(R) guideline (*11*).

These approaches range from simple formulas for calculating the percentage of total peak area to complex formulas that incorporate correction factors. Correction factors are incorporated to adjust for differences in concentrations between test and reference standard solutions, molecular weights of different forms of a compound, and detector response.

Percent of Total Peak Area

An example of the simplest formula follows:

$$100(r_i / r_s),$$

where r_i is the peak response for each impurity observed in the *Test solution* and r_s is the sum of responses for all peaks in the *Test solution*. Multiplying by 100 converts the result to the desired units of percent. The experimental design uses data from a test solution only; there is no concomitant analysis of a reference standard solution. This formula assumes similar detector responses for all peaks in the chromatogram. Examples of this formula are found in the drug substance monographs for Fenoldapam Mesylate and Pheniramine Maleate. Execution of this simple experimental design and formula can also be applied to drug product monographs as shown in the monographs for Fluoxetine Capsules and Gadodiamide Injection.

Using Different Concentrations of the Test Sample

The next level of complexity in terms of experimental design and formula used to quantitate impurities involves the use of test solutions prepared at different concentrations. The goal of this design is to maximize the peak response of impurities by using a concentrated test sample solution. For quantitation purposes, a less concentrated solution of the test sample is needed because the response of the major peak in the concentrated test sample solution typically is off-scale (overrange in an electronic data system); thus the peak response of the major peak is inaccurate. This experimental design is reflected in the formula by accounting for the difference in the two test sample solutions from which data are used.

Following is an example from the Fluoxetine Hydrochloride monograph. This procedure requires the preparation and analysis of two fluoxetine hydrochloride solutions: *Test solution 1* is 5.6 mg per mL and *Test solution 2* is prepared by a 5-fold dilution of *Test solution 1*.

$$100r_i(r_s + 5r_U),$$

in which r_i is the peak response from each impurity obtained from *Test solution 1;* r_s is the sum of all peak responses, excluding that of fluoxetine, obtained from *Test solution 1,* and r_U is the peak response of fluoxetine obtained from *Test solution 2*. *Test solution 1* is 5 times the concentration of *Test solution 2,* so the factor of 5 is needed in the formula to account for this difference. It should be noted that this factor is not explained in the monograph along with the other terms of the equation but rather it is based on knowledge of the experimental design.

Using a Reference Standard

Moving to the next level of complexity in experimental design involves examining procedures in which impurities in the test sample are quantitated against a reference standard solution. In this type of experiment, impurities may

be quantitated against a reference standard of the parent compound or against an appropriate related compound reference standard. The formula for calculating the amount of a related compound must consider whether or not the determination is made against a corresponding reference standard of the impurity.

In *Related compounds Test 2* of the Pyrilamine Maleate monograph, the percentage of each impurity is calculated against the USP Pyrilamine Maleate RS as follows:

$$10{,}000(C/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Pyrilamine Maleate RS in the *Standard solution, W* is the weight, in mg, of the Pyrilamine Maleate taken to prepare the *Test solution,* r_i is the peak response for each impurity, and r_S is the response of the *Standard solution*. It should be noted in this example that although the units of the target concentration given in the instructions for the preparation of the *Standard solution* are in µg per mL, the concentration term in the formula is defined as mg per mL. Therefore, it is necessary to convert the concentration of the *Standard solution* to mg per mL by dividing the concentration in µg per mL by 1,000. Another feature of this formula is the term of 10,000 which is not explained in the monograph. Based on the experimental design, the dimensional analysis shows:

$$\% = \frac{\left(\frac{mg}{mL}\right)\left(\frac{area_i}{area_S}\right)(100mL)(100\%)}{mg}$$

Written in this manner, C is the concentration of the *Standard solution* in mg per mL, the response of r_i and r_S are represented as $area_i$ and $area_S$, respectively, and W is the weight, in mg, of the test sample. To complete the calculation, the term 100 mL is added to the numerator because the sample weight, *W,* is diluted to 100 mL according the test solution preparation. The term 100% is needed to convert the result to percent. The terms mg, mL, and area cancel, leaving 100 × 100, or 10,000.

With some exceptions, multipliers appearing in formulas are not explained. Readers familiar with *USP* monographs are accustomed to seeing factors such as 10,000 or 50,000 in formulas without a specific explanation. The reason for this is the understanding that the multiplier reflects a combination of factors reduced to a single term. Although the purpose of the multiplier has been to simplify the formula for the reader, this practice may not be optimal because the derivations of these factors are not always clear. An experienced user of *USP* monographs can usually derive these numbers, but often it is a time-consuming exercise. In the interest of providing useful information, formulas in monographs should include an explanation of all terms and avoid condensing terms. One way to avoid unexplained multipliers is to include the concentration terms because the purpose of the multiplier is to account for the dilution factors. Examples of this approach include the Mefanamic Acid, Methylprednisone Hemisuccinate, Phenytoin, Phenytoin Sodium, Propantheline Bromide Tablets, and Proparacaine Hydrochloride Ophthalmic Solution monographs. Although the terms may vary slightly, the format for the formulas for calculating the percentage of related compounds is:

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, typically in mg per mL, of the *Standard solution;* C_U is the theoretical concentration of the *Test solution* (same units as the *Standard solution*); and r_U and r_S are the peak responses from the *Test solution* and *Standard solution,* respectively.

A variation of this format is used when the concentrations of the *Test solution* and *Standard solution* are expressed in different units, e.g., µg per mL for the *Test solution* and mg per mL for the *Standard solution*. Maintaining the same straightforward approach, the formula for calculating the percentage of related compounds becomes:

$$0.1(C_S/C_U)(r_U/r_S),$$

in which the C_S is the concentration, in µg per mL, of the *Standard solution;* C_U is the concentration, in mg per mL, of the *Test solution; and* r_U and r_S are the peak responses of the *Test solution* and *Standard solution,* respectively. In this case, the multiplier of 0.1 represents the 100% divided by the factor of 1000 necessary for the conversion of µg per mL to mg per mL. Examples of this format are included in the *Related compounds* procedures for the Hydroxyzine Hydrochloride and Methsuximide monographs.

Using Relative Response Factors

When the quantitation of an impurity is performed using a reference standard other than the impurity reference standard, typically the API reference standard, a relative response factor (RRF) may be used. An RRF value, which is specific to a given set of experimental conditions, compares the responses of the impurity and the API reference standard and is incorporated into the formula as a means to correct for differences in detector response.

This technique is used in the following formula for calculating related compounds in the Zileuton drug substance monograph.

$$100F(C_S/C_U)(r_i/r_S),$$

in which F is the relative response factor for each impurity 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*.

In *USP* monographs, placement of the RRF in the numerator or denominator depends on how RRF was determined. If the RRF was calculated using the ratio of the impurity response relative to that of the API, then the

RRF appears in the denominator. The RRF appears in the numerator if it was calculated as the response of the API to that of the impurity. Currently, there is no USP definition for determining an RRF value; however USP is working to develop a definition and incorporate it consistently in all monographs.

As stated in General Chapter *Validation of Compendial Methods* ⟨1225⟩, in the absence of other information, it may be necessary to calculate the amount of an impurity based on a 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. When using a response factor in a formula, one should understand that the value is applicable only to the experimental conditions defined in the procedure (*12*).

When a reference standard is indicated in a procedure, it may be the same compound as the test sample or it may be different, e.g., the free base of a compound versus the salt form. Adjustments for molecular weight differences between different forms of an impurity or parent drug (free base versus salt form) are incorporated into the formula (see the *Assay* section of this article for examples). Having the molecular weight terms clearly presented and defined is crucial to a *Related compounds* test. The calculation of the percentage of impurities in the Propoxyphene Hydrochloride monograph includes a factor of 1.12, which is the ratio of the molecular weights of α-*d*-2-acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane hydrochloride to that of α-*d*-2-acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane free base; the individual molecular weights for these two compounds are not provided in the monograph.

RECOMMENDATIONS

Based on a review of formulas used in current *USP* monographs, the following suggestions are offered in order to provide the most information and facilitate use of the monograph:

1. Present formulas so that all terms, including numerical terms, and their units are included and defined for the user.
2. Avoid condensing several terms into a single multiplier. If a condensed multiplier must be used, its origin should be clearly explained in the monograph.
3. For calculation of related compounds, include a concentration term for the sample under test because it incorporates dilution factors, thereby reducing the need for an unexplained multiplier in formulas.
4. Include relative response factors and relative retention times in the monograph if corresponding reference standard materials are not available.
5. Change the format of formulas in current *USP* monographs in accordance with points 1–4 above. Revisions should be made as early as possible.
6. For the *Assay,* formulas should be written so that the final results are expressed in the same units as the assay limits presented in the definition, unless otherwise specified in the monograph.
7. Create a new General Chapter for the pharmaceutical calculations used in the *USP* monographs. The content of this *Stimuli* article, after comments from the industry and other stakeholders, is expected to be the basis for this chapter. This General Chapter should provide an easy reference for further clarification of the calculations used in *USP* monographs.

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HPLC Column Classification

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ABSTRACT This *Stimuli* article represents the conclusions and recommendations of the USP Working Group on HPLC Columns. The working group included the five largest manufacturers of HPLC columns in the United States, along with the National Institute of Standards and Technology (NIST) and USP. This work attempts to facilitate the selection of HPLC columns by the analyst when performing a USP test.

INTRODUCTION

The L nomenclature to designate high-performance liquid chromatography (HPLC) column type was introduced for the first time in the *Fourth Supplement* to *USP XIX* in 1978. The L1 designation is for columns with octadecilsilane as the bonded phase. When *USP XX* was published in 1980, only seven columns were classified and given a brief description. Since then the list has grown without pause to 56 descriptions, some of them very broad or with imprecise wording (*1, 2*). For years, this classification system has generated an increasing number of inquiries to USP regarding which column brand is appropriate for a particular compendial procedure. Today, column packings are developed for specific applications, resulting in columns with distinct characteristics even though they belong to the same original USP classification. For example, more than 220 columns currently available in the worldwide market can be classified as L1, but not all of them have the same applications (*3, 4*). This situation makes the process of selecting a column for a particular application very difficult. The problem is partially controlled by the *System Suitability* test in most of the USP chromatographic procedures, but in many cases these tests are not conclusive to ensure column interchangeability. Evidently the current classification nomenclature does not provide sufficient information to fill the needs of modern liquid chromatography.

THE USP APPROACH

In an attempt to facilitate the selection of possible columns by the analyst, the chair of the USP Expert Committee (EC) on Pharmaceutical Analysis 2, Dr. Timothy Wozniak, and the vice-chair of the same EC, Dr. Linda Ng, created a group to define a proposal about how to subclassify initially only L1 columns, and, perhaps in the future, extend the approach to other USP column designations. The USP Working Group on HPLC Columns was created, and its membership represented the National Institute of Standards and Technology (NIST) and the five largest manufacturers of HPLC columns in the United States. Dr. Ng chaired this group.

At the beginning the group considered several existing approaches. After a series of meetings, they decided to use the NIST Standard Reference Material (SRM) 870 to carry out the evaluation of C18 columns according to the procedure described in the certificate of analysis for this SRM (*5, 6*).

This procedure uses a mixture of five organic compounds (uracil, toluene, ethylbenzene, quinizarin, and amitriptyline) in methanol to characterize column performance. This test mixture is intended primarily for the characterization of C18 columns used in reversed-phase liquid chromatography. Selection of the components in SRM 870 was based on published testing protocols (*7, 8*) and commercial column literature (*9*) to provide a broad characterization of column performance in a single, simple test.

On the basis of the results obtained and the problems faced during the evaluation of the C18 columns using NIST SRM 870, the group identified four parameters to be used in the characterization of the columns: hydrophobicity (capacity factor of ethylbenzene); chelation (tailing factor of quinizarin); activity toward bases (silanol activity, capacity factor, and tailing factor of amitriptyline); and shape selectivity (bonding density). The term *shape selectivity* is commonly used to denote a chromatographic quality exhibited by certain stationary phases for which enhanced separations of geometric isomers may result based on their molecular structure rather than other physical or chemical properties of the solute (*10*). Although SRM 870 does not characterize shape selectivity, the property can be assessed by use of other chromatographic tests, such as SRM 869a, *Column Selectivity Test Mixture for Liquid Chromatography,* or by measuring the bonding density of the stationary phase.

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To compare columns on the same basis, the user should evaluate column performance by separating the mixture isocratically using a mobile phase constituted by 80% methanol and 20% buffer phosphate at pH 7.0.

The certificate of analysis for NIST SRM 870 contains a series of chromatograms representative of possible types of retention behavior. In most instances, peak identification can be made on the basis of elution order (uracil, toluene, ethylbenzene) and detector response (quinizarin, amitriptyline). Relative peak areas depend on the detection wavelength. Quinizarin has significant absorbance at 480 nm, and separations of SRM 870 carried out at this wavelength are selective for this single component. Conversely, quinizarin exhibits reduced absorbance at 210 nm, permitting measurement of amitriptyline in the presence of quinizarin.

The retention behavior of reversed-phase liquid chromatography (LC) columns often differs in a variety of ways. The components in this test mixture were selected as indicators of several types of chromatographic properties. The determination of peak width (efficiency; theoretical plates), peak asymmetry (A_S), absolute retention (k'), and selectivity factor (α, i.e., relative retention, k'_1/k'_2) for these components may provide useful measures of these properties.

Uracil

This component is commonly used as an indicator of the void volume (unretained volume) in an LC column, which is required to calculate the retention factor (k').

Toluene/Ethylbenzene

The retention of these compounds can be considered to result primarily from solvophobic interactions. The selectivity factor $\alpha_{E/T}$ is the k' ratio of ethylbenzene and toluene, and this value has been used to characterize differences among C18 and C8 columns. Absolute retention of a nonpolar component such as ethylbenzene provides a measure of column retentiveness (column strength). Toluene and/or ethylbenzene are also useful markers for calculation of column efficiency (theoretical plates, N).

Quinizarin

Quinizarin (1,4-dihydroxyanthraquinone) is a metal-chelating reagent. The retention behavior of this component is expected to be indicative of the presence or absence of metals in the chromatographic system. Columns demonstrate one of two types of retention behavior. Low activity toward chelating reagents is indicated by symmetric peak shape, and high activity toward chelating reagents is indicated by tailing, asymmetric peak shape. Quinizarin typically elutes after ethylbenzene and before amitriptyline. It is interesting to note that for columns known to contain certain embedded polar functional groups, quinizarin elutes last, with good peak symmetry. Peak asymmetry is not strongly correlated with retention for quinizarin.

Amitriptyline

Amitriptyline is a basic compound (pKa = 9.4) commonly used by column manufacturers for column characterization. Elution of organic bases with severe peak tailing is often associated with high silanol activity; however, the elution of such compounds with symmetrical peak shape is considered indicative of column deactivation. Because peak tailing is the most objectionable property associated with silanol activity, A_S is an appropriate measure of this property. Peak asymmetry is not strongly correlated with retention for amitriptyline.

The influence of chromatographic conditions on test results was examined for several different parameters. Because retention, efficiency, and peak shape are influenced by testing conditions, column evaluation should be carried out under standardized conditions to facilitate column comparisons. The largest changes in retention behavior occur with changes in mobile phase composition. The absolute retention of the polar and nonpolar components increases with the percentage of buffer in the mobile phase (at pH 7.0 and constant ionic strength in the mixed solution). A composition of 80% methanol and 20% buffer was selected to provide appropriate retention for a broad range of column types.

Changes in column temperature influence the absolute retention of the components in SRM 870; however, relatively small effects are observed in the peak shape of quinizarin or amitriptyline. It is recommended that column temperature be controlled to 23 °C ±1 °C.

Forty-one commercial C18 columns were used in the development of SRM 870. Columns were selected to represent a broad sampling of chromatographic retention properties and included alkyl phases prepared with embedded polar functional groups. No two columns exhibit identical retention behavior; however, similarities do exist among several columns. Among columns utilized, values of k' for ethylbenzene ranged from 0.2 to 2.8. In contrast, only slight differences were observed for methylene selectivity ($\alpha_{E/T}$; range, 1.26 to 1.45). The retention of quinizarin ranged from $k' = 1$ to $k' = 23.6$. In two instances, no elution of this compound was detected. Peak asymmetry values ranged from $A_S = 1.1$ to $A_S = 5.7$ (in two instances, peaks were not defined well enough to permit determination of A_S). Finally, the retention of amitriptyline ranged from $k' = 1.4$ to $k' = 72.9$ ($A_S = 1.0$ to $A_S = 11$).

Besides the members of the USP Working Group, several other column manufacturers tested their columns using this protocol. The results from these tests are presented in *Table 1*.

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Table 1. Characterization of C18 columns using NIST SRM 870

Column Number	Hydrophobicity Capacity Factor (k') Ethylbenzene	Chelating Tailing Factor Quinizarin	Silanol Activity		Shape Selectivity Bonding Density (μmols/m^2)
			Capacity Factor (k') Amitriptyline	Tailing Factor Amitriptyline	
1	2.8	No peak	No peak	No peak	3.4
2	2.1	1.4	8.2	6.7	3.5
3	2.0	1.1	7.3	2.3	2.0
4	2.4	1.0	6.1	1.8	4.0
5	2.4	1.1	5.9	3.4	3.8
6	1.0	6.0	7.5	4.0	1.1
7	1.5	7.5	4.6	3.0	2.7
8	2.2	1.7	5.1	1.7	3.2
9	1.6	1.5	3.1	1.2	3.3
10	0.7	No peak	23	3.0	1.7
11	2.0	No peak	11.5	7.0	2.6
12	1.0	1.2	1.7	1.1	2.3
13	1.5	1.1	3.3	1.3	2.2
14	2.0	No peak	35	8.0	2.7
15	1.7	1.1	5.1	2.4	1.6
16	2.0	2.0	6.3	1.9	3.5
17	1.5	1.9	23	2.8	2.2
18	1.6	6.6	4.1	2.7	3.2
19	4.2	1.6	11	3.9	3.6
20	3.2	1.6	7.6	2.0	3.6
21	0.9	1.3	2.2	2.1	4.2
22	0.4	2.5	1.0	4.9	Not available
23	1.5	1.5	3.5	2.0	3.1
24	1.5	3.4	4.3	3.6	3.2
25	1.5	2.0	5.6	4.1	2.4
26	1.2	2.2	12	2.6	4.6
27	1.3	1.4	3.5	2.1	3.3
28	2.2	1.2	5.3	1.1	3.4
29	0.7	No peak	2.1	1.4	2.3
30	2.6	1.2	—	3.3	4.0
31	2.2	1.0	—	3.6	Not available
32	2.5	1.6	—	1.2	3.3
33	2.0	1.2	—	1.0	5.5
34	1.0	1.4	3.0	2.6	3.0
35	1.3	No peak	3.8	3.9	3.1
36	1.3	2.0	4.5	13	3.1
37	1.8	1.5	13.6	2.8	2.6
38	1.9	1.5	5.0	2.4	2.6
39	1.9	1.5	5.1	2.4	2.7
40	1.9	1.5	6.0	2.9	2.2
41	3.3	1.3	8.8	2.9	3.2
42	1.6	1.4	5.0	2.7	1.4
43	0.9	1.4	3.0	2.8	0.9
44	1.9	1.3	5.0	1.5	2.5
45	1.5	1.3	4.4	1.9	1.9
46	3.3	1.2	7.5	1.3	3.0
47	2.0	1.0	6.7	2.6	2.1
48	1.0	2.2	3.1	2.4	2.1
49	2.2	1.4	14.2	3.5	3.2
50	2.2	1.8	10.2	2.2	3.0
51	3.9	1.7	12.5	4.0	2.9
52	2.3	1.0	6.1	1.8	2.9

Table 1. Characterization of C18 columns using NIST SRM 870 *(Continued)*

Column Number	Hydrophobicity Capacity Factor (k') Ethylbenzene	Chelating Tailing Factor Quinizarin	Silanol Activity		Shape Selectivity Bonding Density (μmols/m^2)
			Capacity Factor (k') Amitriptyline	Tailing Factor Amitriptyline	
53	1.1	1.7	2.9	2.2	2.9
54	0.7	1.6	2.2	2.7	2.9
55	2.0	1.2	3.8	1.6	2.8
56	1.1	1.2	2.2	1.2	3.2
57	0.7	1.3	1.4	1.8	3.2
58	2.6	1.5	1.7	—	—
59	0.6	1.5	1.7	—	—
60	2.0	1.1	4.0	1.1	3.2
61	3.4	1.1	13.5	5.4	2.8
62	2.0	1.0	23.0	4.5	2.6
63	0.4	1.4	14.5	3.5	1.2
64	1.4	1.3	4.3	5.3	5.2
65	2.6	1.4	7.8	1.9	3.3
66	2.1	1.2	5.7	1.5	3.3
67	0.8	1.5	3.1	2.9	3.3

Figure 1 illustrates typical elution patterns for SRM 870. To improve chromatographic performance toward bases, five of the columns utilized are known to contain embedded polar functional groups within the stationary phase. The separation of SRM 870 was similar for these columns. In each case, quinizarin eluted last, and both amitriptyline and quinizarin exhibited symmetrical peak shape (e.g., *Figure 1A*).

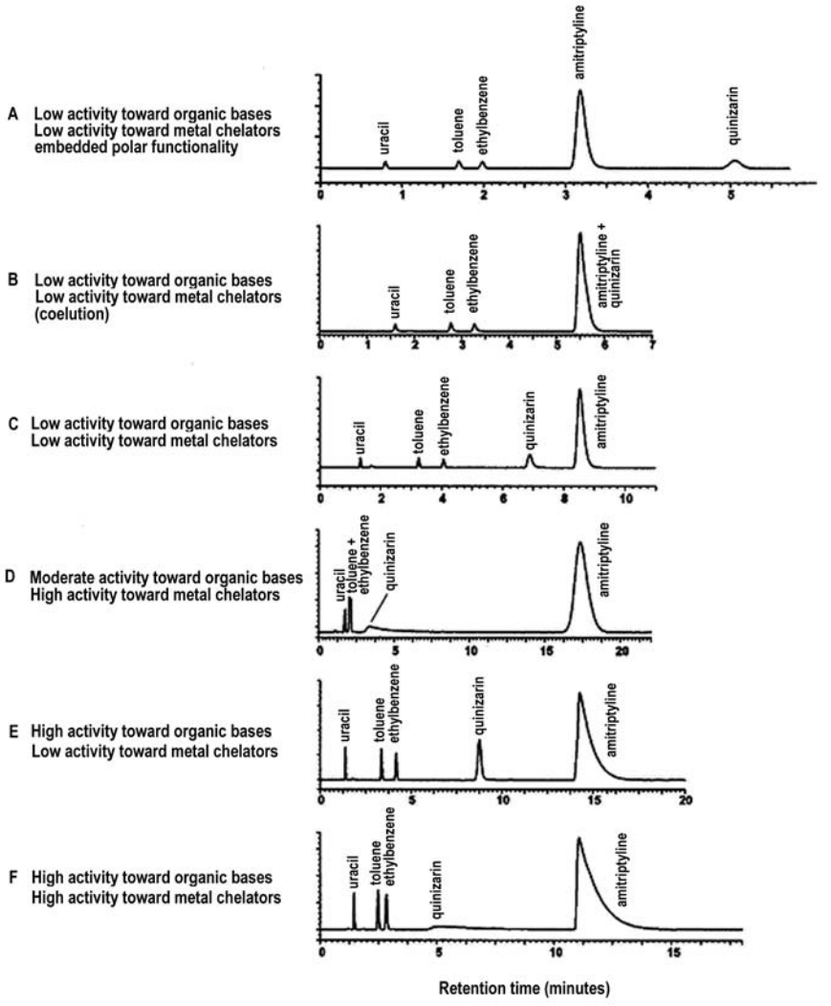

Fig. 1. Examples of separations of SRM 870 on commercial C18 column (reproduced from SRM-870 Certificate of Analysis, NIST)

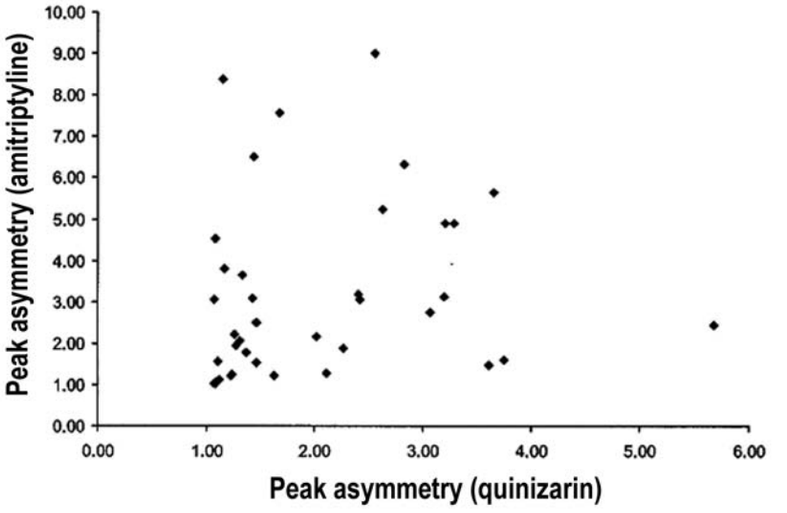

Fig. 2. Plot of peak asymmetry for amitriptyline vs. peak asymmetry for quinazirin for various C18 columns (reproduced from SRM-870 Certificate of Analysis, NIST)

Peak asymmetry data for quinizarin and amitriptyline are plotted in *Figure 2*. The scatter in the data indicates independence of the two terms. Thus, it is possible for a column to exhibit high activity toward chelating agents and low activity toward bases, or other combinations (e.g., *Figures 1C* through *1F*).

THE PQRI INITIATIVE

The Impurities Working Group of the PQRI Drug Substance Technical Committee had an objective to investigate the impact of technology on the characterization of impurities. This project is being carried out in collaboration with Dr. Lloyd Snyder, who has initiated work to create a database and software that will help to define conditions that will lead to equivalent separations for different columns. An application resulting from the project will be a way to obtain an equivalent separation for a monograph method that stipulates an L1 or L7 column.

The Snyder/Dolan column test procedure has been described in a series of publications (*11–18* and a review in *19*). Based on retention data for a series of standard mixtures (see *Table 2*) and the same separation conditions (50% acetonitrile/buffer; pH 2.8 and 7.0; 35 °C), every reversed-phase column can be characterized by six column-selectivity parameters (*15*): relative retention (k_{EB}), hydrophobicity (*H*), steric interaction (*S**), hydrogen-bond acidity (*A*) and basicity (*B*), and relative silanol ionization or cation-exchange capacity (*C*).

Table 2. Test mixtures for Snyder/Dolan procedure

Mixture 1 thiourea amitriptyline 4-butylbenzoic acid	**Mixture 2a** nortriptyline acetophenone mefenamic acid
Mixture 1a *N,N*-diethylacetamide 5-phenyl-1-pentanol ethylbenzene	**Mixture 3** *p*-nitrophenol anisole 4-hexylaniline
Mixture 2 *N,N*-dimethylacetamide 5,5-diphenylhydantoin toluene	**Mixture 3a** *cis/trans* chalcone benzonitrile
	Mixture 4 berberine

Column *hydrophobicity* increases with an increase in total carbon. *H* is somewhat larger for small-pore packings because of the compression of the ends of the alkyl chains. Because end-capping adds only a few tenths of a percent carbon to the column, end-capping has little effect on *H*. As noted before, *H* has only a minor effect on column selectivity.

Column *steric interaction* increases as the bonded phase becomes more crowded. That means an increase in *S** for increased chain length or concentration of the bonded phase. *S** also increases for narrow-pore packings because of the compression of the ends of the alkyl groups. *S** has a significant effect on column selectivity, especially for molecules of different shape.

Column *hydrogen-bond acidity* due to non-ionized silanols increases with column acidity. Therefore, values of *A* are greater for more acidic type-A columns. When the column is end-capped, the number of accessible and unreacted silanols decreases, as do values of *A*. The column parameter *A* has a significant effect on column selectivity for non-ionized basic molecules such as amines and amides, especially aliphatic derivatives.

Column *hydrogen-bond basicity* arises from various functional groups within the bonded phase. For all type-B (high-purity silica) and some type-A (older, less pure silica) columns, it appears that water from the mobile phase partly dissolves in the bonded phase, and this water can preferentially interact with and bind to non-ionized carboxylic acids. So, columns with larger values of *B* preferentially retain acidic compounds.

In the case of columns with embedded polar groups, the basic polar group (urea, amide, carbamate) can strongly bind both phenols and carboxylic acids. Some type-A columns have larger values of *B,* believed to be the result of metal impurities in the silica.

Silanol ionization results in a negative charge on the column, and this charge attracts ionized (positively charged) bases and repels ionized (negatively charged) acids. For samples that contain ionized acids or (especially) bases, the column parameter *C* is a very important contributor to column selectivity. For samples that do not contain acids or bases, *C* is unimportant. Column ionization and values of *C* increase as mobile-phase pH is increased. End-capping results in decreased access to ionized silanols and a large decrease in *C*.

The ability to characterize column selectivity is of potential value for two different situations. First, routine HPLC procedures require the replacement of the column from time to time due to deterioration of the column during use. Also, when an HPLC method is transferred, it is necessary to obtain a suitable column for that procedure. In either situation, there exists the possibility that an equivalent column from the original supplier may no longer be available. For this reason, two or more equivalent columns with different part numbers can be specified as part of method development. ''Equivalent'' columns will have similar (ideally, ''identical'') values of the six column-selectivity parameters discussed above. This phase of the project was done and completed in collaboration with PQRI.

A second use of the six column-selectivity parameters outlined above is for the selection of columns of very different selectivity. Columns of different selectivity are often required during HPLC method development (for a deliberate change in selectivity) or for the development of orthogonal procedures that can be used to ensure that no new sample impurity is present in some samples.

The Snyder/Dolan procedure was originally developed for application to type-B C18 columns (*11–13*). It since has been extended to type-B alkyl–silica columns with C_1–C_{30} ligands (*14*), type-A C8 and C18 columns (*15*), columns with polar groups such as urea, carbamate, or amide that are either embedded into the ligand or used to end-cap the column (*16*), cyano columns (*17*), and phenyl and fluoro columns (*18*).

Columns with identical values of *H, S*, A, B*, and *C* are expected to give essentially identical selectivity (spacing of bands) for a given HPLC procedure (same mobile phase, temperature, and flow rate). Small differences in values of k_{EB} can be corrected by changes in flow rate. Although it is rare to find two reversed-phase columns that have identical values of *H, S*,* etc., small differences in these column parameters are still acceptable for any sample, and larger differences are allowable for some samples. A column comparison function F_S can be defined for two columns 1 and 2 as follows:

$$F_S = \{[12.5\ (H_2 - H_1)]^2 + [100\ (S^*_2 - S^*_1)]^2 + [30\ (A_2 - A_1)]^2 + [143\ (B_2 - B_1)]^2 + [83\ (C_2 - C_1)]^2\}^{1/2} \qquad [1]$$

Here, H_1 and H_2 refer to values of *H* for columns 1 and 2, S^*_1 and S^*_2 are values of *S** for columns 1 and 2, and so on for the remaining column parameters *A, B,* and *C*. If $F_S<3$ for any two columns 1 and 2, the two columns should provide equivalent selectivity and band spacing for any sample or set of conditions. Equivalent separation may still be achieved for $F_S>3$, but this is less certain. However, if it is known that the sample does not contain ionized compounds (e.g., no acids or [especially] bases), the term $C_2 - C_1$ of Equation 1 can be ignored, which usually means a much smaller value of F_S for two columns 1 and 2. Similarly, if carboxylic acids (ionized or not) are absent from the sample, the term $B_2 - B_1$ can also be ignored, again reducing the value of F_S.

In the event that columns of very different selectivity are desired, two columns 1 and 2 with a very large value of F_S would be preferred. *Figure 3* provides an example of the use of values of F_S to select columns of either similar (*a–c*) or different (*d*) selectivity.

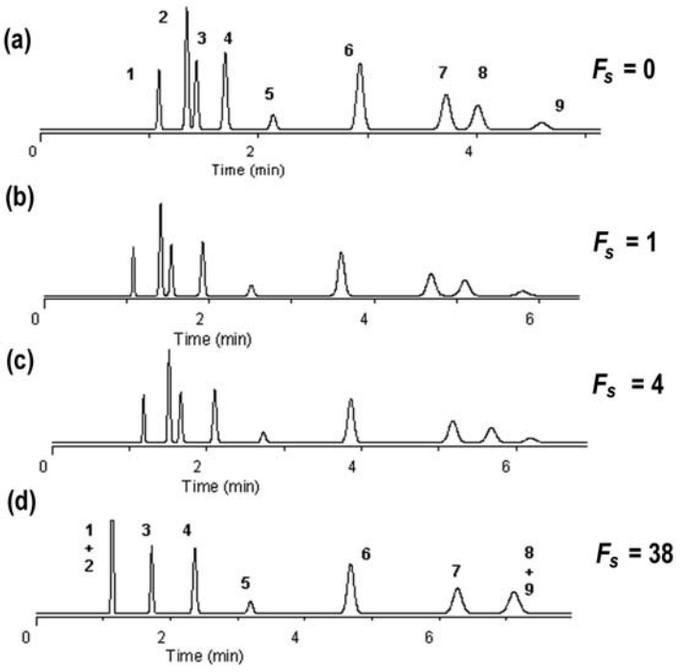

Fig. 3. Example of use of F_S values to select columns of either similar (*a–c*) or different (*d*) selectivity

The measurement of values of *H, S*,* etc. has been studied by four separate laboratories under PQRI sponsorship. On the basis of replicate testing of 42 different C8 and C18 columns, it was established that the measurement of values of *H, S*,* etc. is suitably repeatable (*20*). Further studies by these and other laboratories have since confirmed the reliability of Equation 1 as a basis for comparing column selectivity (*21*). These results have substantiated the ability of values of F_S to select columns of equivalent selectivity. The study of Snyder et al. (*20*) has also shown that the measurement of values of *H, S*,* etc. can be simplified and shortened, requiring only 2–3 hours per column. Five separate laboratories are currently evaluating the utility of the Snyder/Dolan approach for the development of orthogonal separations.

CONCLUSIONS

Both of these approaches have merit, and it is too soon to favor one over the other. The USP approach provides column performance characterization (theoretical plate count, good peak symmetry, etc.) and produces five data points to describe the column. The PQRI approach provides selectivity characterization (relative retention times), and the parameters are included in a searchable database that produces a list of suitable columns ordered by the F_S factor. The USP approach also could be provided in database form to permit ordering of columns based on a single factor derived from the measured parameters (analogous to the Snyder/Dolan approach). A third option might be to provide data from both characterization approaches. Algorithms could be developed to permit column assessment based on the combined data. Ultimately, the approach(es) utilized must balance ease of use with effectiveness.

In the USP approach, performance proprieties include tailing determination due to the presence of trace metals in the column packing and "active" silanols (which may also be the result of metal contamination), but the PQRI (Snyder/Dolan procedure) does not. However, it must be pointed out that poor column performance is associated mainly with older columns that utilize type-A silica.

As a result of the evaluation presented here, the USP Working Group on column classification resolved to publish the data obtained by these two approaches and encourage users to submit their comments in order to improve these tools. In the near future, the results obtained by the NIST SRM 870 and the searchable database will become public via the USP Web page (www.usp.org). This will allow users to evaluate the results obtained with both approaches. Both databases will be updated as new results are obtained. In the interim, USP will continue to update and publish *Chromat-*

ographic Reagents Used in USP–NF and Pharmacopeial Forum that lists the original column brand used during method development for compendial procedures.

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Isonicotinyl Hydrazone of Rifampicin and Isoniazid: Should It Be Controlled as a Related Substance (or Impurity) in USP Monographs for Anti-tuberculosis Combination Products?

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ABSTRACT A significant amount of rifampicin is converted to isonicotinyl hydrazone (HYD) in the presence of isoniazid in the formulation environment and also in situ under stomach acid pH conditions. The present study was carried out to determine whether this interaction product should be included as a related substance (or impurity) in USP monographs for combination products containing these two drugs. For this purpose, the in vivo fate and the chemotherapeutic activity of HYD were determined. The stability of HYD was determined at various gastrointestinal pH conditions, in various tissue homogenates, and in the blood of rats. The samples were analyzed by a validated HPLC method. In vitro activity was determined against *Mycobacterium tuberculosis* H37Rv. In vivo activity was tested against the same microorganism by administering the compound to Laca mice via oral and intravenous routes at three dose levels (4, 12, and 24 mg/kg).

HYD was rapidly hydrolyzed at pH <3 and also in intestinal homogenate and blood. In all these cases, the hydrolysis products were 3-formylrifamycin and isoniazid. Although HYD showed in vitro activity at a concentration of 6 μg/mL, 3-formylrifamycin, the hydrolysis product of HYD, showed activity at 0.6 μg/mL. However, both these compounds were found to be devoid of in vivo activity, except that 3-formylrifamycin showed activity at 24 mg/kg after intravenous administration. The study shows that to whatever extent rifampicin is converted to HYD, the result is a corresponding loss of anti-tuberculosis activity. Thus, it may be reasonable to suggest that HYD should be controlled as a related substance or an impurity in the USP monographs for anti-tuberculosis combination products containing rifampicin and isoniazid.

INTRODUCTION

The fixed-dose combinations (FDCs) of anti-tuberculosis (anti-TB) drugs (rifampicin, isoniazid, pyrazinamide, and/or ethambutol) are being promoted by the World Health Organization in its worldwide programs because of the obvious advantages of patient compliance, prevention of monotherapy, etc. (*1*). However, several reports in the literature have raised concerns about the quality of these products, and more FDCs have been found to be substandard than have single-drug formulations (*2–4*). There are even reports about decreased bioavailability of rifampicin in drug combinations (*5–7*). Several meetings also have been held in the recent past to discuss the quality of FDCs and to find solutions to the problems (*8–10*). The USP Drug Quality Information (USP DQI) program recently held a meeting in Botswana regarding the quality of anti-infectives in use and recommended a three-level testing system for ensuring the quality of FDCs. Among the recommendations, one of the elements was the determination of unusual impurities (*10*).

Research in our laboratory has confirmed that there is indeed an unusual impurity generated in anti-tuberculosis FDC products and that it is formed not as a result of degradation of either drug present in the combinations but rather from the interaction between rifampicin and isoniazid, the two primary anti-TB drugs. The drugs show facile interaction to form isonicotinyl hydrazone (HYD) in situ under stomach acid conditions (*11–12*) and also in the solid-state environment of unpackaged and packaged FDC formulations (*13–14*). This is amply shown from the data in *Table 1*. The mechanisms for the decomposition of rifampicin in the presence of isoniazid under both acidic and nonacidic formulation conditions have been postulated.

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Table 1. Typical extents of decomposition of rifampicin and isoniazid and formation of HYD on exposure of pure drugs in acid medium and on storage of marketed packaged and unpackaged FDC products under accelerated conditions

Drug combinations	Conditions/Package type	% Decomposition R	% Decomposition H	Area % of HYD*
Pure drug mixtures exposed to acidic pH conditions at 37 °C†				
R + H	pH 1.0 for 60 min	10.6	4.0	3.7
	pH 1.5 for 60 min	22.5	6.5	9.9
	pH 2.0 for 15 min	11.9	4.8	—
	pH 2.0 for 60 min	33.8	9.9	12.6
	pH 2.0 for 3 h	62.6	11.1	—
Packaged marketed anti-TB FDC products exposed to accelerated conditions of 40 °C/75% RH for 3 months‡				
R + H	Strip	5.7	4.8	3.3
	Blister	6.3	8.8	1.9
R + H + Z	Blister	22.4	10.4	12.5
R + H + E	Strip	19.7	26.4	4.3
	Blister	31.5	12.1	26.4
R + H + Z + E	Strip	18.1	25.5	4.9
	Blister	19.7	6.6	17.4
Unpackaged marketed anti-TB FDC products exposed to accelerated conditions of 40 °C/75% RH for 3 months‡				
R + H	Strip	11.7	36.2	19.1
	Blister	26.6	46.3	8.9
R + H + Z	Blister	83.8	90.4	44.5
R + H + E	Strip	93.7	73.5	67.1
	Blister	91.4	70.5	74.4
R + H + Z + E	Strip	97.5	81.0	81.3
	Blister	93.1	82.2	73.7

Key: R—Rifampicin, H—Isoniazid, Z—Pyrazinamide, E—Ethambutol.

* The area % of HYD was calculated with respect to *R* and *H,* ignoring the contribution due to *Z*. The contribution due to *E* was not measured because it was not analyzed by the HPLC method.

† Data taken from reference 12.

‡ Data taken from reference 14.

It has been proposed that under acidic conditions rifampicin is hydrolyzed to 3-formylrifamycin, which interacts with isoniazid to form HYD by means of a fast second-order reaction. The product, due to its instability in acidic conditions, regenerates isoniazid and 3-formylrifamycin by a pseudo–first-order reaction. Because the second-order forward reaction is faster than the preceding (rifampicin to 3-formylrifamycin) and the following (hydrazone to 3-formylrifamycin and isoniazid) first-order reactions, the overall reaction is favored towards the formation of hydrazone. As a result, the decomposition of rifampicin to 3-formylrifamycin is pushed forward, and an overall enhancement of degradation of rifampicin is observed (*15*). Under non-acidic formulation conditions, the reaction takes place through a transhydrazone formation process via nucleophilic attack on the imine group of rifampicin by the amino group of isoniazid following a tetrahedral mechanism (*16*). Because these reactions result in extensive loss of rifampicin and to a smaller or equal extent even of isoniazid (*Table 1*), this has been held as the reason behind the quality and bioavailability problems with FDC products (*17*).

However, even though this interaction affects the quality of anti-TB FDCs, USP, which is the first international pharmacopoeia to establish standards for anti-tuberculosis combination products (*18*), still does not cover isonicotinyl hydrazone as a related substance or an impurity. Recently, USP carried out a survey regarding studies and literature reports on FDC drugs (*19*), as a result of which hydrazone was recognized as an unstable product formed from rifampicin in the presence of isoniazid, which is a positive development.

However, a formal declaration of hydrazone as a related substance or impurity perhaps requires key information about its fate in vivo, as well as a determination about whether or not it possesses anti-TB activity. The present study was carried out to find answers to these questions.

MATERIALS AND METHODS

Materials

Sprague-Dawley rats used in the studies were in the weight range of 240–260 g. Laca mice were in the weight range of 20–25 g. All studies involving the use of animals were carried out under approved protocols from Institutional Animal Ethics Committees. *Mycobacterium tuberculosis* H37Rv was obtained from the National Collection of Type Cultures (NCTC), London, UK. Rifampicin and isoniazid were gift samples from Panacea Biotec Ltd., Lalru, India. HYD was prepared by an already reported method (*15*). Buffer materials and all other chemicals were of analytical-reagent grade. HPLC-grade acetonitrile and methanol were procured from J.T. Baker (Mexico City, Mexico) and Mallinckrodt Baker Inc. (Paris, KY, USA), respectively. Ultrapure water was obtained from a water purification unit (Elga Ltd., Bucks, England). Culture media and other chemicals for microbiological studies were obtained from Himedia Laboratories Pvt. Ltd., Mumbai, India.

Equipment

Decomposition studies were carried out using a digital shaking water bath (Julabo SW21, Seelbach, Germany). pH recordings were made on a research pH meter (MA 235, Mettler Toledo GmbH, Schwerzenbach, Switzerland). Other equipment used included an analytical balance (AG 135, Mettler Toledo, Switzerland), autopipettes (Tripette, Merck KGaA, Darmstadt, Germany), a homogenizer (PT-MR 3100 POLYTRON, Kinematica AG, Littau, Switzerland), a sonicator (Branson Ultra-sonic Corporation, Danbury, CT, USA), and a centrifuge (Biofuge 15, Hanau, Germany). The HPLC system consisted of an on-line degasser (DGU-14AM), low-pressure gradient flow control valve (FCV-10AL$_{VP}$), solvent delivery module (LC-10AT$_{VP}$), autoinjector (SIL-10AD$_{VP}$), column oven (CTO-10AS$_{VP}$), UV-visible dual-wavelength detector (SPD-10A$_{VP}$), system controller (SCL-10A$_{VP}$) and CLASS-VP software (all from Shimadzu, Kyoto, Japan). The separations were achieved on a Zorbax XDB C-18 (250 × 4.6 mm, 5 µm) column (Agilent Technologies, Wilmington, DE, USA).

Stability at Different pH Level

HYD was added to buffers with pH between 1.0 and 7.0 at a concentration of 0.8 mg/mL. The resulting suspensions/solutions were stored at 37 °C for 1 hour. The samples were analyzed by HPLC after appropriate dilution with methanol. Percentage degradation was calculated from the difference between the peak areas of samples drawn at 0 and 1 hour.

Stability of HYD in Homogenates of Rat Gastrointestinal Tract (GIT) and Liver

Necessary organs (stomach, intestine, and liver) were removed from rats and retained in ice-cold saline until homogenization. The organs were homogenized before the study, and the masses were diluted to 10% with phosphate buffer (pH 7.4) and stored at –20 °C. HYD at a concentration of 50 µg/mL was added to dilute homogenates, and the mixtures were incubated at 37 °C in a shaking water bath set at 50 rpm. At appropriate intervals, 250-µL samples were withdrawn and mixed with 750 µL of methanol to cause protein precipitation. Subsequently, centrifugation was carried out at 5000 rpm, and the supernatant was analyzed by HPLC. All the studies were carried out in triplicate.

Stability of HYD in Rat Blood

Kinetics studies were conducted on HYD in whole rat blood at the same drug concentration and following a similar incubation and testing protocol, as described above for homogenates of GIT and liver.

HPLC Analyses

HYD was analyzed by HPLC employing a gradient method reported earlier (*20*). The mobile phase was composed of acetonitrile and buffer consisting of 0.01 M sodium dihydrogen orthophosphate (pH adjusted to 6.8 with dilute orthophosphoric acid). The method was validated for the parameters such as linearity, precision, and accuracy.

In Vitro Anti-Mycobacterial Activity

Testing for in vitro activity was carried out on HYD and also 3-formylrifamycin. Rifampicin and isoniazid were tested as controls. The established broth microdilution minimum inhibitory concentration (MIC) method (*21*) was employed using *M. tuberculosis* H37Rv. The procedure involved addition of different concentrations of the compounds from the stock solutions to flasks containing 100 mL Youman's medium. Subsequently, 500 µL of *M. tuberculosis* H37Rv culture containing 1.5×10^8 colony-forming units (cfu) per mL was added. The flasks were kept in a shaker for 7 days. On the eighth day, growth was observed visibly in all the flasks and compared to the blank. The lowest concentration of the drug at which the surface growth layer could not be observed was taken as the MIC.

In Vivo Anti-Tubercular Activity

This experiment was carried out using the method reported by Pandey et al. (*22*). Laca mice were infected through the tail vein with 1×10^5 viable bacilli of *M. tuberculosis* H37Rv in 0.1 mL of sterile isotonic saline. To confirm the establishment of infection, three animals were randomly selected and sacrificed after 15 days. Their lungs and spleens were removed aseptically and homogenized in

sterile phosphate buffered saline (PBS). Ziehl Neelsen staining of tissue smears confirmed establishment of the infection. In addition, 50 µL of undiluted homogenates were plated on Middlebrook 7H10 agar base supplemented with oleic acid, dextrose, and citrate (OADC). Colonies were counted three weeks post-inoculation, and basal cfu load was calculated.

For the treatment, mice were organized into thirteen groups, including the control (Group I). Groups II to VII were used for testing 3-formylrifamycin, and Groups VIII to XIII were used for HYD. The compounds were dissolved in a mixture of water and methanol (4:1), and 0.1 mL was administered intravenously and also orally for 14 days at doses of 4, 12, and 24 mg/kg. On the 15th day, the mice were sacrificed, and their livers and spleens were removed and homogenized. The homogenates were plated after appropriate dilution, as described above. Colonies were counted on day 21 post-inoculation.

RESULTS AND DISCUSSION

Figure 1 shows the pH–stability profile of HYD. It clearly shows that HYD is labile in the acidic pH range but is stable beyond pH 5. The profile can be attributed to hydrogen-ion catalysis and noncatalysis of the hydrolysis of the undissociated compound (*23*). A review of the chromatograms generated during stability studies confirmed that HYD was converted to 3-formylrifamycin and isoniazid upon degradation, because peaks relative to these two appeared with the progress of the reaction.

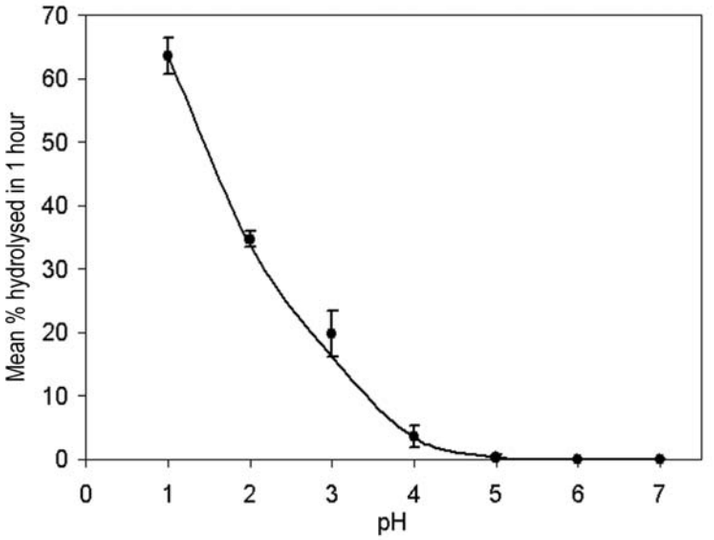

Fig. 1. pH–stability profile of HYD at 37 °C. Results are expressed as the mean ±SD of at least three experiments.

Pseudo–first-order plots for the hydrolysis of HYD in homogenates of rat stomach, intestine, liver, and rat blood are given in *Figure 2.* The corresponding hydrolysis rate constants and half-lives are listed in *Table 2.* HYD hydrolyzed in blood and tissue homogenates in the order of intestine>blood>liver>stomach. Also in these studies, the chromatogram showed conversion of HYD to 3-formylrifamycin and isoniazid. This suggests that HYD has a good potential to rapidly reconvert to 3-formylrifamycin and isoniazid inside the body.

Table 2. Pseudo–first-order hydrolysis rate constants and half-lives of HYD in various GI segments, liver, and blood of rat

Homogenate/ blood	Rate constant, k ($hour^{-1}$)	Half life (hours)
Stomach	0.092 ±0.001	7.56 ±0.08
Intestine	0.471 ±0.009	1.47 ±0.03
Liver	0.129 ±0.001	5.34 ±0.06
Blood	0.229 ±0.004	3.03 ±0.06

Results are expressed as the mean ±SD of at least three experiments.

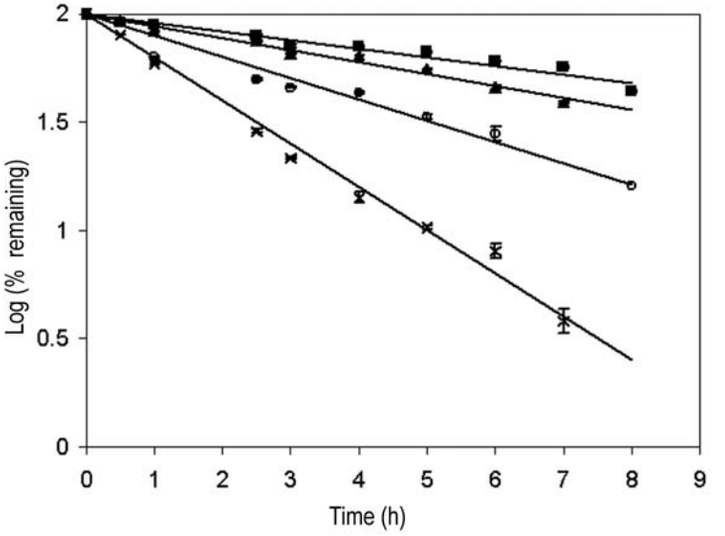

Fig. 2. Pseudo–first-order plots for the hydrolysis of HYD in rat stomach (■), intestine (×), and liver (▲) homogenates, and blood (O). Results are expressed as the mean ±SD of at least three experiments.

Table 3 lists the MIC values of rifampicin, isoniazid, 3-formylrifamycin, and HYD. The values given in the table for rifampicin (0.25 μg/mL) and isoniazid (0.1 μg/mL) are similar to those reported in the literature (*21, 24*), confirming that the method used for in vitro testing was dependable and could give reproducible results. By the same test, the MIC value obtained for 3-formylrifamycin was 0.6 μg/mL, and the corresponding value for HYD was 6.0 μg/mL.

Table 3. In vitro anti-tubercular activities of rifampicin, isoniazid, 3-formylrifamycin, and HYD against *M. tuberculosis* H37Rv

Compound	Concentration ranges tested (μg/mL)	MIC (μg/mL)	Relative potency with respect to rifampicin
Rifampicin	0.05–1.0	0.25 (0.06–0.25)*	—
Isoniazid	0.05–1.0	0.10 (0.025–0.3)	2.5
3-Formylrifamycin	0.05–1.0	0.60	0.416
HYD	0.05–10.0	6.00	0.0416

* Values in the parentheses are literature values (*21, 24*).

Table 4 shows the in vivo chemotherapeutic efficacy of 3-formylrifamycin and HYD when administered by intravenous and oral routes. As evident, 3-formylrifamycin was active only after intravenous administration of the highest tested dose of 24 mg/kg. It was inactive orally at all tested doses. On the other hand, HYD was devoid of in vivo activity when administered by both intravenous and oral routes.

Table 4. In vivo anti-tubercular activities of 3-formylrifamycin and HYD administered via intravenous and oral routes

Groups	Route of administration	Dose (mg/kg)	Log_{10} cfu/lung	Log_{10} cfu/spleen
Basal	—	—	2.552 ±0.042	2.439 ±0.059
Control				
I	—	—	4.864 ±0.031	4.844 ±0.023
3-Formylrifamycin				
II	Intravenous	4	4.765 ±0.016	4.773 ±0.018
III		12	4.703 ±0.016	4.732 ±0.026
IV		24	4.085 ±0.071*	4.008 ±0.067*
V	Oral	4	4.845 ±0.020	4.858 ±0.027
VI		12	4.871 ±0.022	4.852 ±0.024
VII		24	4.834 ±0.022	4.857 ±0.019
Isonicotinyl hydrazone (HYD)				
VIII	Intravenous	4	4.817 ±0.014	4.789 ±0.017
IX		12	4.849 ±0.019	4.873 ±0.014
X		24	4.872 ±0.024	4.765 ±0.016
XI	Oral	4	4.826 ±0.024	4.814 ±0.015
XII		12	4.788 ±0.028	4.820 ±0.025
XIII		24	4.864 ±0.026	4.852 ±0.024

Results are expressed as the mean ±SEM of at least six experiments.
* Significantly different from control ($p<0.001$).

CONCLUSION

This study provides a clear conclusion that any extent of HYD that may be present initially in anti-tuberculosis FDC formulations containing rifampicin and isoniazid or is formed in situ in the stomach upon administration of these products would result in a loss of therapeutic activity of rifampicin, the first-line drug for tuberculosis. This is because HYD lacks in vivo activity, and even its conversion to 3-formylrifamycin does not help because the latter is also inactive in vivo; 3-formylrifamycin has also been mentioned previously in the literature as an inactive metabolite of rifampicin (*25*). Thus it may be necessary to control the presence of HYD in formulations for which compendial authorities, especially USP, should consider categorizing HYD as a related substance. To assess and control the extent of in situ conversion of rifampicin and isoniazid to HYD, it may be prudent to include in the compendia an additional test for dissolution. This dissolution test could involve the determination of the extent of HYD formed from anti-tuberculosis combination formulations in 0.01 M hydrochloric acid (pH ~2) at 37 °C in 1 hour (*17, 26*), the mean stomach residence time. USP at present recommends dissolution testing in 0.1 M hydrochloric acid (pH ~1) for 45 minutes for a two-drug combination, simulated gastric fluid for 30 minutes for a three-drug combination, and pH 6.8 for 45 minutes for four-drug combinations. It is reported that interaction between rifampicin and isoniazid takes place much more strongly at pH 2 than pH 1 (*12*). For analysis of dissolution samples for all these combinations, the use of HPLC methods is suggested, unlike the colorimetric method recommended currently in USP for testing dissolution samples of two- and three-drug combination products containing rifampicin and isoniazid. Our recent separate findings are that HYD interferes in colorimetric (*27*) and microbiological (*28*) methods of analysis of rifampicin.

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RSD and Other Variability Measures of the Lognormal Distribution

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ABSTRACT This *Stimuli* article reviews relative standard deviation (RSD) in the context of the lognormal distribution. The article discusses the advantage of RSD compared to standard deviation (SD). Other variability measures that offer similar advantage are discussed and compared.

The relative standard deviation (*RSD* or *%RSD*) is defined as the sample standard deviation, *S,* divided by sample mean, $\overline{X}$, and is expressed as a percentage:

$$RSD = \frac{S}{\overline{X}} \times 100\%.$$

It is a widely used measure of variability in biology and chemistry. *RSD* is sometimes referred to as the coefficient of variance *(CV)* in many statistics textbooks and is little studied in statistics. The purpose of this *Stimuli* article is to describe the characteristics of the *RSD,* particularly in the context of the lognormal distribution.

In biology and, to a lesser degree, in chemistry, the variability of a measurement often increases with the magnitude of the measurement. In many cases, the log-transformed measurements are well characterized or approximated by normal distributions. In such cases, the original measurement is said to have the lognormal distribution with the following density function:

$$f(x) = \frac{1}{\sqrt{2\pi}\sigma} * \frac{\exp\left(-(\ln x - \mu)^2 / (2\sigma^2)\right)}{x},$$

$$\text{where } \ln x = \log_e x,$$

where μ is the mean and σ is the standard deviation of the normal distribution, and x is any point on the distribution. The mean and standard deviation of the lognormally distributed variable X are

$$E(X) = \exp\left(\mu + \sigma^2/2\right),$$

and

$$std(X) = \exp(\mu)\sqrt{\exp\left(2\sigma^2\right) - \exp\left(\sigma^2\right)}.$$

The *RSD* of the lognormally distributed X is

$$RSD(X) = std(X)/E(X) * 100\% =$$

$$\sqrt{\exp\left(\sigma^2\right) - 1} * 100\%.$$

It is worth noting that *RSD* of X depends only on one parameter, σ, but both the mean and standard deviation of X depend on both parameters, μ and σ.

A normal distribution is completely specified by its natural location and variability parameters: mean and standard deviation. The two parameters are also ‘‘independent’’ in the sense that by changing one parameter without changing the other, one still has a valid normal distribution. The mean and standard deviation of the lognormal distribution are not ‘‘independent’’ in this sense, because a higher mean demands a higher standard deviation. However, there are ‘‘independent’’ location and variability parameters that completely specify a lognormal distribution.

Many statistical procedures were developed under the assumption that the population from which the sample is taken is normally distributed. Pooling the variability estimates at different response levels is an important part of many statistical procedures, including analysis of variation (ANOVA),

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regression, and variance component analysis. For lognormal distributions, the standard deviations are not poolable when the means are different; however, alternative parameters do exist to allow pooling of variability across response levels. For example, the *RSD*s can be pooled when the medians are different.

The median of the lognormal distribution, $median(X) = \exp(\mu)$, is a location parameter that is a meaningful alternative to the mean. There are several alternative variability parameters that are independent of the median; the *RSD* is one. Other choices include

$$R_2 = [\exp(\sigma) - 1] * 100\%,$$

and

$$R_3 = \sigma * 100\%.$$

R_2 is particularly useful in constructing intervals with specified probability. The following interval covers the lognormal distribution with the same probability as that for the usual interval $[\mu - k\sigma, \mu + k\sigma]$ covered in the normal case:

$$\left[\frac{\exp(\mu)}{(R_2 + 1)^k}, \exp(\mu) \times (R_2 + 1)^k \right].$$

R_3 is simply the standard deviation on the log-transformed scale.

It is interesting to note that *RSD*, R_2, and R_3 are numerically very close when they are small: The three are within 2% of each other when they are less than 20%. This may explain why they are often treated as if they are the same parameter. *Table 1* compares the three variability parameters numerically.

Table 1. Comparison of *RSD*, R_2, and R_3

RSD	0.00%	5.00%	10.00%	15.00%	20.00%	25.00%
R_2	0.00%	5.12%	10.49%	16.09%	21.90%	27.92%
R_3	0.00%	5.00%	9.98%	14.92%	19.80%	24.62%
RSD	35.00%	40.00%	45.00%	50.00%	60.00%	70.00%
R_2	40.49%	47.00%	53.64%	60.38%	74.11%	88.04%
R_3	33.99%	38.53%	42.94%	47.24%	55.45%	63.15%
RSD	80.00%	90.00%	100.00%	120.00%	140.00%	160.00%
R_2	102.05%	116.04%	129.92%	157.14%	183.41%	208.59%
R_3	70.33%	77.03%	83.26%	94.45%	104.17%	112.68%

When lognormal distributions are appropriate, many classic and commonly used statistical procedures (e.g., ANOVA) can be performed on the log-transformed data. The arithmetic mean of the log-transformed data corresponds to the geometric mean (GM) of the original data, which is an estimator for the median. The difference in the log scale becomes a ratio in the original scale. The variance of the log-transformed data can be easily translated to *RSD* or R_2 on the original scale.

If the information obtained from an assay is considered to be normally distributed, and

$$\sigma^2_{between} \text{ and } \sigma^2_{within}$$

are the between-run and within-run variance components, respectively, then the total variability of a single readout from this assay is

$$\sigma^2_{total} = \sigma^2_{between} + \sigma^2_{within}.$$

Similarly, if the readout from an assay is considered to be lognormally distributed, and $RSD_{between}$ and RSD_{within} are the between-run and within-run *RSD*s, respectively, then the total *RSD* of a single readout from this assay is

$$RSD^2_{total} + 1 = (RSD^2_{between} + 1)(RSD^2_{within} + 1).$$

If the reportable value of the assay in the normal case is the mean of n runs and k replicates per run, the precision variance of the reportable value is

$$\sigma^2_{precision} = \frac{\sigma^2_{between}}{n} + \frac{\sigma^2_{within}}{n*k}.$$

Similarly, if the reportable value of the assay in the lognormal case is the geometric mean of n runs and k replicates per run, the precision *RSD* of the reportable value is

$$RSD^2_{precision} + 1 = \left(RSD^2_{between} + 1\right)^{\frac{1}{n}} * \left(RSD^2_{within} + 1\right)^{\frac{1}{n*k}}.$$

It should be noted that the *RSD,* R_2, and R_3 defined above apply only when the log of base e (natural log) is used in the transformation. If log of base 10 (common log) is used, they should be modified as

$$RSD = \sqrt{\left(10^{\ln 10}\right)^{\sigma^2} - 1} * 100\%,$$

$$R_2 = (10^{\sigma} - 1) * 100\%,$$

and

$$R_3 = \ln 10 * \sigma * 100\%.$$

In conclusion, the standard deviation is the natural variability parameter for normal distribution but not for all distributions. In the context of lognormal distribution, which is common in biological and chemical measurements, *RSD* and R_2 may be more useful.

NOTE 1

If X is lognormally distributed, the inference regarding *RSD* of X can be easily handled by many common statistical procedures applied on the scale of $\ln(X)$. However, if X is normally distributed, inference regarding *RSD* of X is possible, but it is much more complicated.

NOTE 2

Solid dosage pharmaceuticals such as tablets and capsules usually are manufactured only to a few selected strength levels. For assays that measure the active ingredients, the variability does tend to increase with the strength levels (label claims) if the results are reported on the scale of mass/weight. However, if the results are analyzed on the scale of percent label claim, i.e., mass or weight divided by label claim, the variability becomes stable and poolable. In this context, the arithmetic mean, instead of geometric mean, is usually used to average. In other words, normal distributions on the scale of percent label claim usually work well. Sometimes, the standard deviation on the scale of percent label claim is called *RSD*. This is a pseudo-*RSD* because it is not divided by the random variable $\overline{X}$ but by a constant: label claim. However, this pseudo-*RSD* usually is preferred instead of the true *RSD* because it usually provides adequate description of the variability, it is more stable, and there are many readily available statistical procedures to handle the inference.

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The USP Revision Process: Recommendations for Enhancements

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ABSTRACT The International Conference on Harmonization (ICH) defines a specification as "a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. 'Conformance to specifications' means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria" (*1*). The United States Pharmacopeia (USP) is an independent standards-setting organization responsible for publishing the specifications and test methods that govern the strength, quality, and purity of pharmaceutical products of commerce sold in the United States of America. It is recognized as the legal standard by the U.S. Food and Drug Administration (*2–5*) as well as by regulatory authorities in other countries. USP relies on a system of volunteerism to effect changes to these standards, making it distinctive among the compendia. This *Stimuli* article will explore ways to improve the efficiency and timeliness of the *USP* revision process while preserving and strengthening its unique approach to public participation.

INTRODUCTION

The United States Pharmacopeia (USP) has many strengths that set it apart from pharmacopeias of other nations. Because it is the only major nongovernmental pharmacopeia, USP relies on expert volunteers from academia, government, and industry to make decisions about revisions to *USP* text. All changes adopted in *USP* are presented for public review and comment in *Pharmacopeial Forum (PF)*, and significant changes in content are not made without further publication in *PF*, offering additional opportunity for public review. Although the *USP* revision process is efficient, the increasing volume of changes and the expectations of regulatory agencies require enhancement of the basic revision process. In response to its stakeholders' suggestions, USP sponsored a Project Team on Process Improvements, which is made up of representatives from pharmaceutical manufacturers, FDA, and USP staff. This *Stimuli* article discusses the team's observations regarding the current USP process and presents specific recommendations for improvements. The underlying theme of the recommendations is that the comment and implementation periods for a change to a *USP* standard should be a function of the nature of the specific change.

The USP standards-setting process has many facets. It may begin with resolutions proposed at the USP Convention or as information submitted by independent parties, persons, or companies. It may encompass *Stimuli to the Revision Process* articles and participant input from Open Conferences or USP Meetings. Regardless of their origin, proposals for change are published in *PF* before they are officially adopted in the *USP* annual main volume, a semiannual *Supplement,* or a bimonthly (*6*) *Interim Revision Announcement (IRA)*. The processes governing these three publications areas—*PFs, Supplements*/main volumes, and *IRAs*—could benefit from improvements that would positively impact the efficiency of *USP* and the synergy with industry trends and standards.

PHARMACOPEIAL FORUM

The *General Notices and Requirements* section of *USP* describes *PF* as "...the working document of the USP Committee of Revision. It is intended to provide ... public notice of proposed new and revised standards of the *USP* and *NF* and to afford opportunity for comment thereon." This information is echoed in the Standards Development section of *PF* itself: "*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)*."

USP's comment period for *PF* proposals is currently defined to be a minimum of 60 days before the proposal can be officially adopted. The beginning of the comment period starts with the publication of *PF* and includes the transit time for the volume to reach subscribers. Companies can minimize time delays by subscribing to the online version of *PF*. Proposals appearing in *PF* prompt companies and any other users (e.g., academia, health care practitioners, trade associations, health authorities, and governmental agencies such as FDA) to assess the impact these changes could have on products and/or processes before an appropriate, science-based response can be communicated to USP.

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This evaluation must consider the effect of the change in relationship to product quality, release, and stability requirements, as well as regulatory commitments. The evaluation should encompass a comprehensive review for changes to specifications, methodology, associated standard operating procedures, and other relevant documentation (e.g., impact on validation). Many *PF* proposals require a laboratory evaluation before a company can prepare a response. When a laboratory evaluation is warranted, appropriate materials (e.g., reagents, chromatographic columns, and reference standards) must be secured before the analysis. A determination regarding the depth of the evaluation also must be considered in the assessment. Once the appropriate actions for response are determined, the evaluating facility must be identified, and testing must be scheduled and prioritized into the laboratory's daily workload.

The data generated from the laboratory analysis must then be reviewed and comments formulated, approved, and communicated to USP. The final step in the process often results in documents to be edited in anticipation of the proposal being officially adopted in the *USP* main volume or a semiannual *Supplement.* The entire evaluation process ranges from 12 to 180 working days, depending on the complexity and impact of the proposal (see *Figure 1*). It should be noted that the number of proposals a company must address varies from *PF* to *PF* and from company to company and can influence the timeline for evaluation and response. In addition, many companies are not able to complete an entire evaluation of one *PF* before the next one is published.

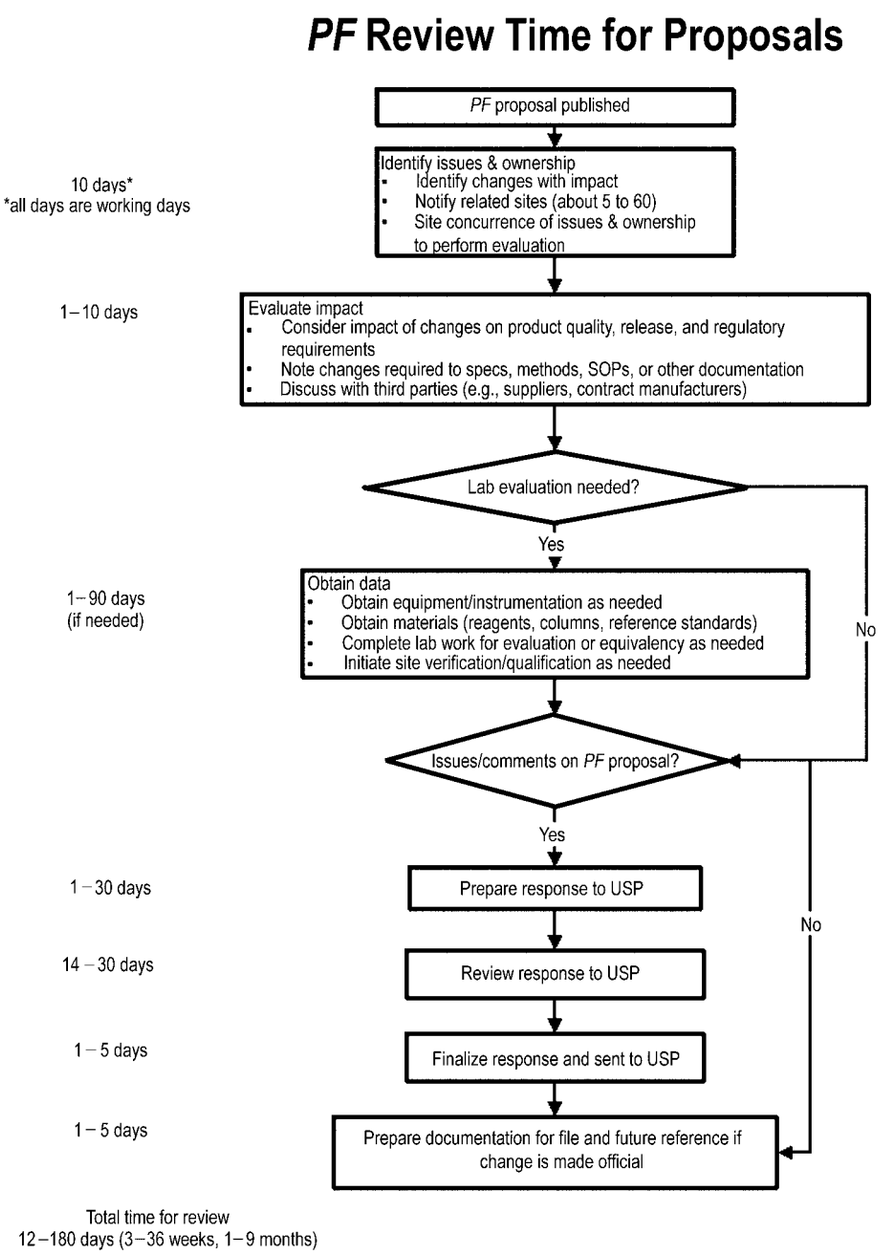

Fig. 1. *PF* review time for proposals

Regulatory authorities also monitor *PF* proposals, and although they face different challenges than does industry, the resulting impact on the resources is similar. Regulators assume the entire contents of *PF* must be reviewed, sorted, and distributed to the appropriate divisions, who in turn must reprioritize their workload to address the impact of the proposal. In an organization as diverse as FDA, finding the appropriate reviewer for a specific issue may take considerable time. In addition, as in industry, FDA staff may have different opinions regarding an issue, and these must be resolved before a comment can be communicated to USP.

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Recommendation

In view of the factors discussed above and the criticality of appropriate review of *PF* proposals, the team recommends assigning comment periods based on the complexity of the proposal. Therefore, instead of targeting all proposals in a particular *PF* to a particular *Supplement* or main volume, a targeted *Supplement* or main volume could be chosen based on the impact of the proposal. For example, a change to a test's acceptance criteria in a particular monograph would be targeted for the next available *Supplement,* thereby triggering a shorter comment period. However, a change to a General Chapter—such as *Residue on Ignition* ⟨281⟩ that influences how we test many compendial articles—would be targeted for a subsequent *Supplement,* thereby allowing more time for laboratory evaluation. In addition, the minimum comment period should be extended from 60 days to 90 days. Most *PF*s allow at least 90 days for comments, but the March–April *PF* allows only about 60 days for comments. An adequate comment period for most proposals (i.e., excluding high-impact changes) could be achieved simply by extending the comment deadline for the March–April *PF* to at least 90 days and leaving the deadlines for the other five *PF*s unchanged.

THE MAIN VOLUME AND *SUPPLEMENTS*

The main volume of *USP,* published yearly, is the current, officially recognized collection of standards that pharmaceutical articles must meet before they can be marketed in the United States. *Supplements* to the main volume are published semiannually. *PF* proposals approved by the Council of Experts are elevated to official status with their inclusion in one of these publications.

The time allowance for implementing changes appearing in a *Supplement* or main volume is currently two months or 60 calendar days from the date of release of publication. As with *PF,* the transit time to receive the publications is deducted from the initial time allowance, thus reducing the amount of time to implement to about 45 calendar days. Again, users of *USP* can minimize the delay by subscribing to the *USP–NF* online version. Once an item becomes official, companies must update their internal control documents to maintain compliance status and to be aligned with the compendium. Changes to official company documents must be completed through a rigorous change-control system. Document changes must be prepared, routed for approval, assigned an effective date, distributed to manufacturing plants and suppliers, and potentially include training before compliance to the new standard can be achieved. This process can take anywhere from 24 working days, for the simplest changes, to 158 working days for the more complex, broad-scope changes such as changes to a General Chapter that impacts many materials (see *Figure 2*). Even if documents are edited for change at the *PF* stage, compliance still may not be achieved by the official date because of the sequential steps needed to ensure adherence to the new standard. Additionally, it may not be practical or beneficial to edit documents at the *PF* stage because subsequent revisions may be made before the change becomes official. In some instances, companies are required to file Changes Being Effected Supplements (CBE-30s) with FDA before the manufacturer can make the change effective, which adds an additional 30 days to an already tight compliance timeline.

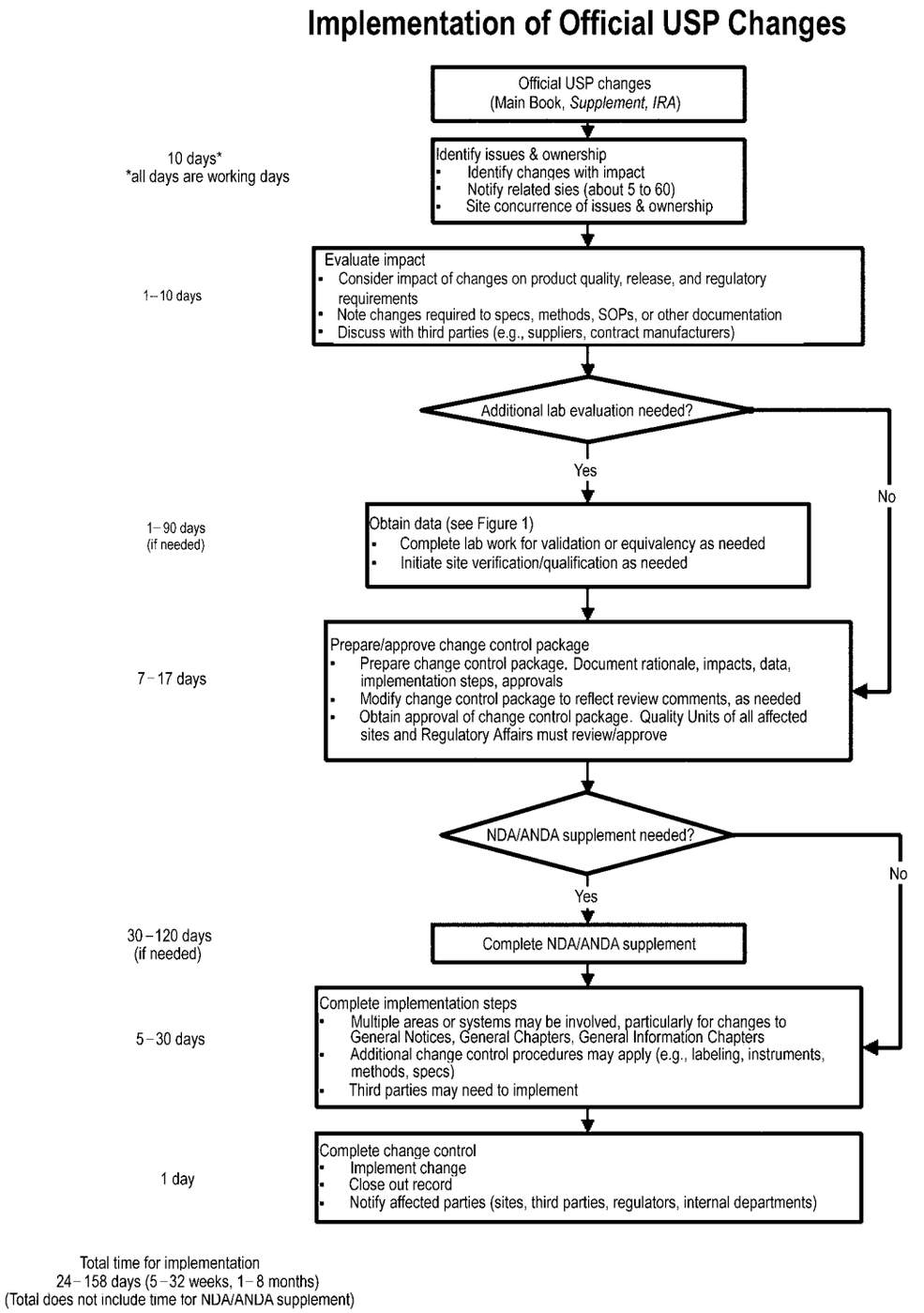

Fig. 2. Implementation of official USP changes

Recommendation

To avoid unnecessary risk to a company's compliance status, the team recommends that USP implement official dates that reflect the scope of the change being adopted. The appropriate time for changes should be chosen on a risk basis. Simple changes (e.g., editorial, editorial clarification) could remain at the current two-month time frame. More complex changes (e.g., specifications or methodology) should have a 6-month time frame for implementation. For broad-scope initiatives (e.g., General Test Chapters, Nomenclature, or Packaging and Storage Requirements) affecting multiple materials or products, a minimum of 12 months should be allowed before the revision becomes effective. Industry must recognize that if these extensions in the implementation timeline for official items are adopted by USP, industry must actively participate and offer recommendations that have been substantiated by data during the *PF* proposal stage. Industry needs to be proactive in reviewing *PF* regardless of the timelines.

INTERIM REVISION ANNOUNCEMENTS

Changes also can be adopted via an *Interim Revision Announcement (IRA)* to allow for rapid implementation of urgent revisions. This type of revision carries the same status as items in *USP–NF* and its *Supplements.* Although *IRA*s may not be published in each edition of *PF,* this typically is the case. Although changes adopted in *IRA*s are considered official, they are always republished in the next *USP–NF* main volume or semiannual *Supplement.*

For industry, *IRA*s carry the same compliance status as the main volume or its *Supplements.* The steps to effect these changes mimic those discussed in the section on main volume and *Supplements,* with the exception that the timeline for implementation is different because they are issued in response to critical need. *IRA*s should encompass very few issues, and industry must be able to implement them quickly. However, even the most responsive change-control system requires adequate time for adopting new standards and conducting training. The current 30-day period is not adequate for industry unless it is willing to enact the new standard on a risk-based decision.

Recommendation

To ensure that all users have equal opportunity to achieve compliance to *IRA* issues, the team recommends that the timeline for an *IRA* to become official should be extended by an additional 15 days, thus bringing the total time for complying with an *IRA* to 45 days. In addition, the team recommends that *IRA*s be used solely to address safety or regulatory compliance issues (i.e., those issues that are truly urgent and require immediate implementation).

ADDITIONAL RECOMMENDATIONS

In addition to the recommendations outlined above, USP should consider additional changes in an effort to bring their process timelines in line with industry's. The *Previews* section of the *PF* should be eliminated, and items that normally would have appeared in this section should be introduced in the *In-Process Revision* section with an extended comment period. The Project Team also recommends that USP publish a work plan for the 2005–2010 revision cycle to allow for more transparency in the process. Moreover, it recommends that a list of standards that have been approved for implementation be published on the USP Web site, along with the targeted *Supplement*/main volume for each item. The list could be further broken down to new and revised text similar to the *Admissions* list in the front of each *Supplement*/main volume.

CONCLUSION

The current USP revision process challenges industry's ability to appropriately respond to ever-changing standards in a timely manner based on the volume and complexity of the issues currently being proposed. The Project Team on Process Improvements recommends that USP modify its current revision timelines by:

1. assigning *PF* comment periods that reflect the complexity of the proposals,
2. assigning official adoption dates that correspond to the complexity of the issues being implemented, and
3. extending the adoption period for an *IRA* issue to 45 days.

We anticipate that USP's adopting the recommendations outlined in this article would positively influence the standards-setting process. USP timelines would be more closely synchronized with industry's ability to react/respond to proposals and adopt USP standards in a timely manner via mandated change control and compliance systems. The recommendations would allow companies to become more proactive and less reactive in setting and maintaining compliance with the public standards governing the pharmaceutical industry.

REFERENCES

1. International Conference on Harmonization. *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. Q6A.* 1999.
2. *FDCA* §501(b).
3. 21 *CFR* 211.194(a)(2).
4. 21 *CFR* 205.50(c).
5. 21 *CFR* 299.4(c), (d), and (f).
6. *IRA*s also are used to announce the availability of new USP Reference Standards and any delay in adoption of procedures using the Reference Standards. For more information regarding contents of an *IRA,* see the *General Notices and Requirements* section of *USP–NF,* subsection *PF.*

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.

Nomenclature

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This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 31(1).

[*Note—This index covers Vol. 31 No. 1, pp. 1–288, Vol. 31, No. 2, pp. 289–669*]

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* The *USP–NF* (*USP29–NF24*), 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:

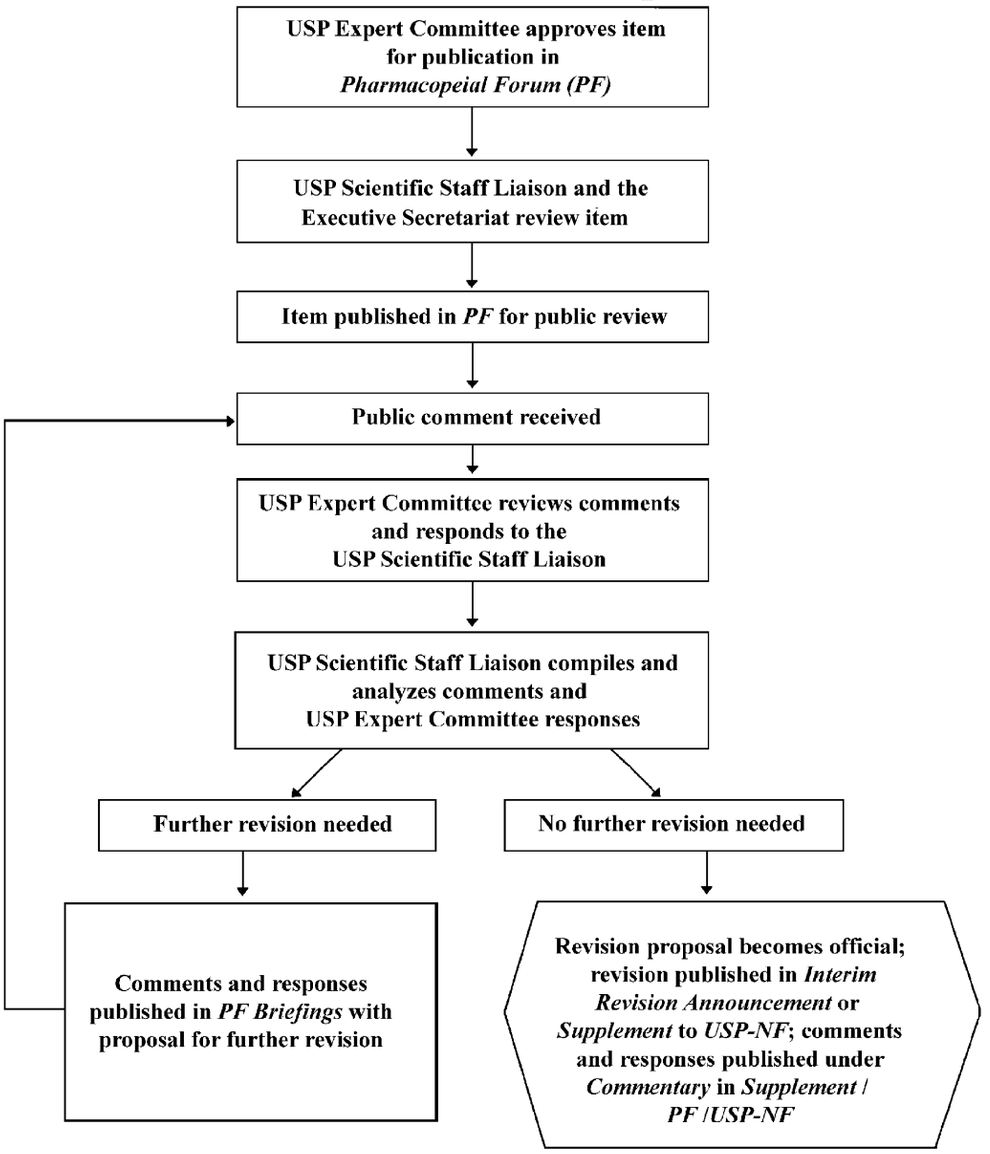
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official 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. 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.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

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

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Cumulative directory for the content of all issues of *PF* beginning with *PF* 31(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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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 7a—Antibiotics; 7b—Antimicrobials and Antivirals
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.

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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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.

POLICY DECISIONS OF THE COUNCIL OF EXPERTS EXECUTIVE COMMITTEE JANUARY 25–28, 2005. The 2000–2005 Council of Experts Executive Committee met for the final time on January 25–28, 2005. The meeting included a joint session with the USP Board of Trustees, end-of-cycle presentations by the Chairperson of the Council of Experts and each Division Executive Committee (Noncomplex Actives and Excipients, Complex Actives, General Policies and Requirements, and Information), discussion of several scientific topics, and voting on policy topics relating to polymorphism, degree of hydration, particle size, specific surface area, impurities, and relative response factor. The issues related to these policy topics have been brought to USP's attention through input into USP's standards-setting process by pharmaceutical companies requesting the need for flexibility in USP's monographs. Because of this input and its relation to USP's mission to provide public monographs that promote the public health and provide good quality pharmaceuticals everywhere, the following policies were approved by the Council of Experts Executive Committee.

These policies are respectfully submitted to readers of *Pharmacopeial Forum* and other interested parties by Eric B. Sheinin, Ph.D., USP Chief Science Officer (acting), and Scientific Liaison to the Council of Experts Executive Committee. Where appropriate, they will be incorporated into the *General Notices* section of *USP 29–NF 24* and into the *USP Guideline for Submitting Requests for Revision to USP–NF.*

Council of Experts Executive Committee Members Attending and Voting

Roger L. Williams, M.D., Chairperson; Darrell R. Abernethy, M.D., Ph.D.; Judy P. Boehlert, Ph.D.; Edward M. Cohen, Ph.D.; James E. DeMuth, Ph.D.; Thomas S. Foster, Pharm.D.; Alexander M.M. Shepherd, M.D.; Saloman Stavchansky, Ph.D.; Lynn C. Yeoman, Ph.D.; Timothy P. Wozniak, Ph.D.

Council of Experts Executive Committee Members Not in Attendance and Not Voting

Marilynn Frederiksen, M.D.; Paul Schiff, Ph.D.; Sally S. Seaver, Ph.D.

Policies Relating to Polymorphism, Degree of Hydration, Particle Size, Specific Surface Area, and Impurities

1. Differing Degrees of Solvation/Hydration

The *USP–NF* now allows the inclusion of differing degrees of hydration/solvation in a drug substance monograph. These monographs include tests, procedures, and acceptance criteria to differentiate the differently solvated materials.

Hereafter, the *USP–NF* will allow differing polymorphic forms with appropriate tests, procedures, and acceptance criteria in drug substance monographs. However, this policy will apply only when the FDA has approved, or has not given any indication that it will not approve, a new drug application for a drug product with a different polymorphic form of the active ingredient than the form used to manufacture the reference listed drug. This approach may result in multiple procedures and/or multiple acceptance criteria for a given test. It also may lead to labeling requirements differentiating the various forms.

2. Differing Impurity Profiles

The *USP–NF* now includes procedures and acceptance criteria in a drug substance monograph for multiple impurity profiles, using the flexible monograph approach. These procedures and acceptance criteria are for profiles for which safety has been evaluated by the FDA.

Hereafter, USP can publish a proposed revision to the impurities test in *Pharmacopeial Forum* even if the sponsor of the *Request for Revision* does not have FDA approval at the time, but is seeking such approval. This policy will not limit FDA's authority to approve drug products for the U.S. market. The monograph will contain a statement that it will become official upon approval of an application by FDA.

3. Unnecessary Testing

The flexible monograph policy allows for the inclusion of tests and procedures that are not applicable to all manufacturers of that article. The *General Notices* of the *USP–NF*currently allows the elimination of testing where a manufacturer knows that the material will pass if tested. However, the *General Notices*also states that an article must pass all tests to be compliant.

Hereafter, the *General Notices* will be appended to include the statement to the effect that "where an impurity test or procedure that is not applicable to all manufacturers of that article is included in a monograph, the test need not be per-

formed if the supplier of the article has demonstrated that the given impurity is not formed by or utilized in the synthetic route used for the manufacture of that article."

Hereafter, where a test or procedure that relates to the physical character of an article (such as a particle size test or specific surface area test) that is not applicable to all manufacturers of that article is included in a monograph, the monograph will indicate that the test need not be performed.

USP Policies Relating to Relative Response Factor

1. USP will use the symbol *F* consistently to designate a Relative Response Factor in General Chapters and monographs, where appropriate.
2. USP will use uniform terminology "Relative Response Factor" in all General Chapters and monographs.
3. USP will include definitions of Response Factor and Relative Response Factor in the *Glossary of Symbols* section of General Chapter *Chromatography* ⟨621⟩.
   a. The definition of Response Factor is peak response per unit mass of analyte.
   b. The definition of Relative Response Factor is ratio of the peak response of an impurity to that of an equal amount of the drug substance. That is, $F = r_i / r_U$.
4. The use of a Relative Response Factor is acceptable only if it is accurate within the linear range.
5. Relative Response Factor values are expressed to two decimal places if <1.0 and to one decimal place if ≥1.0.
6. Rounding off to 1.0 is permitted only if the Relative Response Factor is 0.8–1.2. This will be implemented prospectively only.

PQRI TO SURVEY CURRENT EXCIPIENT CONTROL PRACTICES. Later this year, probably during the second quarter, a working group of the Product Quality Research Institute (PQRI), the joint government/industry/academia research consortium, plans to separately survey U.S. pharmaceutical manufacturers, excipient producers, and excipient distributors for information regarding companies' current excipient control practices to assure excipient safety, quality, and processability. Each survey will be confidential and respondents will not be asked to identify themselves, only their area of business, e.g., finished drug manufacturer, excipient manufacturer, or distributor.

Information received will be compiled by the PQRI Executive Secretariat, and survey replies will not be reviewed by working group members, regardless of their affiliation.

It is hoped that information gathered will provide a more comprehensive view of the types of testing, compendial and noncompendial, which are currently in use throughout the different industry segments to control the chemical and physical properties of materials used in pharmaceutical manufacturing. It is anticipated that this information might be useful in connection with ongoing global harmonization efforts related to setting excipient specifications and determination of an excipient's processability.

If so, all parties involved in PQRI activities will benefit, e.g., industry groups, the USP, and the FDA.

Thus, subscribers to the *USP* are asked to watch for the forthcoming survey and to respond. As noted above, all responses will be blinded and confidential.

USP ANNUAL SCIENTIFIC MEETING, SEPTEMBER 27–30, 2005: IMPACT THE FUTURE OF PHARMACOPEIAL STANDARDS. The USP Annual Scientific Meeting will be held in the Hotel del Coronado, San Diego, California, September 27–30, 2005.

Spread the word. Tell your colleagues and register at: www.usp.org/conferences, 301-816-8134.

The USP 2005 Annual Scientific Meeting is your opportunity to directly contribute to USP's standards-setting processes. Through interaction with USP's scientific staff and Council of Experts, you will help establish standards-setting priorities for the organization and help shape the quality requirements that you must, by law, follow.

Featuring:

NEW! Analytical Validation and Verification of Compendial Methods

Learn about the new USP information in General Informational Chapter ⟨1226⟩ *Verification of Compendial Procedures.* Also includes presentations and workshops on the requirements for evolving analytical validation procedures, including spectroscopic and other physical test methods.

Biologics and Biotechnology Derived Therapies

Interactive discussion on cross-cutting, standards-setting activities currently being undertaken by USP, including validation of bioassays, development of standards for ancillary materials and international activities in biological standardization.

NEW! Dietary Supplements

Learn about the current and future impact of dietary supplement verification and new FDA regulatory initiatives on the marketplace; expansion of General Informational Chapter ⟨2030⟩, *Supplemental Information for Botanicals;* technologies for botanical classification, and identification and analysis of new/emerging/potential dietary supplement ingredients.

Excipients

Interact with USP scientific experts, FDA, industry, and academic experts to discuss the science and related issues of excipients quality, including additives, excipient functionality and its impact on formulation, and multisource excipient equivalence, as well as recent advances in the development of novel excipients.

Making *USP–NF* Work for You

Be among the first to learn about future directions and updates based on resolutions adopted at the 2005 USP Convention and through other USP initiatives.

NEW! Annual Scientific Meeting 2005 Exhibit Program

Network with your colleagues as they showcase what's new and upcoming in the industry.

WHO SHOULD ATTEND:

- USP-NF and USP Reference Standards Users
- Scientists focusing on chemistry, biologics and biotechnology, analytical validation, excipients, and dietary supplements
- Government
- Academia and association representatives
- Regulatory Affairs personnel
- R&D and QC personnel
- Lab supervisors/managers
- Compendial Affairs personnel
- Statisticians
- Technical consultants
- Healthcare practitioners

New and experienced bench chemists who want to better understand the USP process also may wish to attend the "Making *USP–NF* Work for You" track.

SCHEDULE:

Day 1—	September 27, 2005:	Registration
Day 2—	September 28, 2005:	The Annual Scientific Meeting starts with an opening session in the morning followed by Track Session I in the afternoon
Day 3—	September 29, 2005:	Track Session II (morning) and Track Session III (afternoon)
Day 4—	September 30, 2005:	Track Session IV in the morning followed by a "Town Hall" discussion. Meeting adjourns at 12:30 p.m.

Extension Services in Pharmacy at the University of Wisconsin-Madison School of Pharmacy is accredited by the Accreditation Council on Pharmacy Education (ACPE, formerly the American Council on Pharmaceutical Education) as a provider of continuing pharmaceutical education. This program is approved for 15 hours or 1.5 continuing education units (CEUs).

In order to receive credit, pharmacists will be required to complete an Annual Scientific Meeting evaluation form. In addition, pharmacists must complete a statements of credit form for continuing pharmaceutical education participation which will be mailed (by USP) within one month after the meeting. ACPE number: 073-999-05-065-L01.

ADVANCE NOTICE OF UPCOMING OFFICIAL REVISIONS TO THE *USP–NF.* In order to provide as much time as possible for industry to adopt revisions made to the compendia, upcoming official revisions to the *USP–NF* are now being announced on the USP website as soon as they are voted on to become official by the appropriate Expert Committees of the Council of Experts.

Readers are directed to the "Notices" section found in the top right corner of the USP homepage at www.usp.org. By clicking on "Upcoming Official Revisions to the *USP–NF:* Reference Standards Required But Not Available" you are taken to a page where upcoming revisions to the compendia are listed. The information posted includes the title of the item being revised, the *PF* citation where the revision was proposed, and a description of the proposal. In addition, an

e-mail link to the USP Scientific Liaison for each revision is listed in parentheses after the item. The actual content and official date of each revision will be published in either an annual edition, *Supplement,* or *Interim Revision Announcement* and the items are sorted according to the publication in which they are to appear.

In addition, readers will also find a list of new USP Reference Standards that correspond to new *USP–NF* monographs but unfortunately are not yet available. The official dates of any *USP–NF* Standards, tests, or assays that require the use of these Standards are postponed until further notice pending availability of the Standards.

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 Noncomplex 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 courses offer specialized instruction for chemists, scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2005 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

Calendar of Pharmacopeial Education Courses, 2005

Date	Name of Course	Location
May 18	Analytical Method Validation	USP Headquarters, Rockville, MD
July 18 and 19	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
August 12	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
August 17	Analytical Method Validation	USP Headquarters, Rockville, MD
August 18	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
August 19	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
October 19 and 20	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 7	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 8	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	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 PRINT, ONLINE, AND CD.** *USP–NF,* the authoritative reference for official pharmaceutical standards is available in three convenient formats—print, online, and CD. One main edition and two *Supplements* are published each year. The current edition, *USP 28–NF 23*, is official through 2005. Starting with the *Second Supplement* to *USP 28–NF 23,* which will be available in June 2005, the *USP–NF* Online and CD versions will feature several enhancements. The

enhancements include ''My *USP–NF,*'' an exciting new option that lets subscribers customize their use of *USP–NF* by saving frequent searches, creating a unique table of contents, and using other personalization options. To order *USP–NF,* go to www.usp.org or call 1-800-227-8772 or 301-881-0666.

CHROMATOGRAPHIC REAGENTS. Official and proposed chromatographic procedures in the *USP–NF* and *Pharmacopeial Forum (PF)* refer to column reagents only by 'L', 'S', or 'G' designations. The brand names of these reagents are listed in *Chromatographic Reagents.* This book also provides an index of column manufacturers and lists alternative columns that may be used to carry out official procedures. *Chromatographic Reagents* saves chemists and scientists valuable laboratory time spent searching for the right columns to use in testing. *Chromatographic Reagents* is available in print format. The online format of the *USP–NF* includes the latest *Chromatographic Reagents*. To order *Chromatographic Reagents,* go to www.usp.org or call 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.

Publication and Comment Schedule for *USP 28–NF 23*

Publication	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

Publication and Comment Schedule for *USP 29–NF 24*

Publication	Comment Deadline	Publication Date	Official Date
Main Book	May 15, 2005	November 2005	January 2006
Supplement One	October 15, 2005	February 2006	April 2006
Supplement Two	February 17, 2006	June 2006	August 2006

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. 2005	Apr. 1, 2005
PF 31(2) [Mar.–Apr. 2005]	Mar. 2005	Not Applicable
2nd IRA [published in *PF* 31(2)]	Mar. 2005	Apr. 1, 2005
PF 31(3) [May–June 2005]	May 2005	Not Applicable
3rd IRA [published in *PF* 31(3)]	May 2005	June 1, 2005
2nd Supplement	June 2005*	Aug. 1, 2005*
PF 31(4) [July–Aug. 2005]	July 2005*	Not Applicable
4th IRA [published in *PF* 31(4)]	July 2005*	Aug. 1, 2005*
PF 31(5) [Sept.–Oct. 2005]	Sept. 2005*	Not Applicable
5th IRA [published in *PF* 31(5)]	Sept. 2005*	Oct. 1, 2005*
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005*	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005*	Dec. 1, 2005*

* 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 (*USP27*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 27*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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.

THIRD INTERIM REVISION ANNOUNCEMENT to *USP 28* and to *NF 23*

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 June 1, 2005. **Released May 1, 2005.**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of *USF–NF* users.

USP Adipic Acid RS (September 1, 2005)
USP Agnuside RS (November 1, 2005)
USP Alcohol RS (May 1, 2005)
USP Aluminum Sulfate (AS)
USP Amiodarone Hydrochloride RS (July 1, 2005)
USP Amlodipine Besylate RS (May 1, 2005)
USP Ammonium Carbonate (AS)
USP Ammonium Phosphate Dibasic (AS)
USP Ascorbyl Palmitate RS (September 1, 2005)
USP Asparagine Anhydrous RS (November 1, 2005)
USP Asparagine Monohydrate RS (November 1, 2005)
USP Bismuth Subcarbonate RS (September 1, 2005)
USP Bismuth Subgallate RS (September 1, 2005)
USP Bismuth Subnitrate RS (November 1, 2005)
USP Boric Acid (AS)
USP Buproprion Hydrochloride Related Compound B RS (November 1, 2005)
USP Calcium Acetate (AS)
USP Calcium Carbonate (AS)
USP Calcium Chloride (AS)
USP Calcium Hydroxide (AS)
USP Calcium Stearate (AS)
USP Calcium Sulfate (AS)
USP Carboxymethylcellulose Sodium RS (September 1, 2005)
USP Carprofen RS (September 1, 2005)
USP Casticin RS (November 1, 2005)
USP Cellaburate (cellulose acetate butyrate) RS (May 1, 2005)
USP Powdered Cellulose (AS)
USP Corn Oil (AS)
USP Cottonseed Oil (AS)
USP Dehydrated Alcohol RS (May 1, 2005)
USP 2-Deoxy-D-glucose RS (November 1, 2005)
USP Dextran 1 RS (July 1, 2005)
USP Dextran T-10 RS (July 1, 2005)
USP Dibutyl Sebacate (AS)
USP Dichlorvos (AS)
USP Diethanolamine RS (November 1, 2005)
USP Eugenol RS (November 1, 2005)
USP Ferrous Sulfate (AS)
USP Fexofenadine Hydrochloride RS (July 1, 2005)
USP Fexofenadine Related Compound A RS (July 1, 2005)
USP Fexofenadine Related Compound B RS (July 1, 2005)
USP Fluconazole RS (July 1, 2005)
USP Fluconazole Related Compound A RS (July 1, 2005)
USP Fluconazole Related Compound B RS (July 1, 2005)
USP Fluconazole Related Compound C RS (July 1, 2005)
USP Fludeoxyglucose Related Compound A RS (September 1, 2005)
USP Fluvoxamine Maleate RS (November 1, 2005)
USP L-Fucose RS (November 1, 2005)
USP Glacial Acetic Acid (AS)
USP Hypromellose Acetate Succinate RS (July 1, 2005)
USP Indinavir RS (September 1, 2005)
USP Indinavir System Suitability RS (September 1, 2005)
USP Isopropyl Alcohol RS (September 1, 2005)
USP Lactase RS (May 1, 2005)
USP Lactic Acid (AS)
USP Lauroyl Polyoxylglycerides (AS)
USP Loratadine Related Compound A RS (May 1, 2005)
USP Loratadine Related Compound B RS (May 1, 2005)
USP Losartan Potassium RS (July 1, 2005)
USP Lutein RS (September 1, 2005)
USP Magnesium Carbonate (AS)
USP Magnesium Chloride (AS)
USP Magnesium Hydroxide (AS)
USP Magnesium Stearate (AS)
USP Magnesium Sulfate (AS)
USP Mangafodipir Related Compound A RS (July 1, 2005)
USP Mangafodipir Related Compound B RS (July 1, 2005)
USP Mangafodipir Trisodium RS (July 1, 2005)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Meglumine RS (September 1, 2005)
USP Melengestrol Acetate RS (September 1, 2005)
USP Melengestrol Acetate Related Compound A RS (September 1, 2005)
USP Melengestrol Acetate Related Compound B RS (September 1, 2005)
USP Methyl Salicylate RS (September 1, 2005)
USP Monobasic Potassium Phosphate (AS)
USP Monoethanolamine RS (November 1, 2005)
USP Monosodium Glutamate RS (September 1, 2005)
USP Morantel Tartrate RS (September 1, 2005)
USP Nabumetone Related Compound A RS (May 1, 2005)
USP Oleic Acid RS (November 1, 2005)
USP Olive Oil (AS)
USP Omeprazole Related Compound A RS (September 1, 2005)
USP Ondansetron Resolution Mixture RS (May 1, 2005)
USP Palm Oil (AS)
USP Pancuronium Bromide RS (September 1, 2005)
USP Paroxetine Related Compound F RS (May 1, 2005)
USP Paroxetine Related Compound G RS (May 1, 2005)
USP Peanut Oil (AS)
USP Phenothiazine (AS)
USP Phenoxyethanol RS (July 1, 2005)
USP Phenylethyl Alcohol RS (November 1, 2005)
USP Phosphoric Acid (AS)
USP Polysorbate 20 (AS)
USP Polysorbate 40 (AS)
USP Polysorbate 60 (AS)
USP Polysorbate 80 (AS)
USP Potassium Benzoate (AS)
USP Potassium Bitartrate (AS)
USP Potassium Carbonate (AS)
USP Potassium Chloride (AS)
USP Potassium Citrate RS (September 1, 2005)
USP Potassium Iodide (AS)
USP Potassium Nitrate (AS)
USP Dibasic Potassium Phosphate (AS)
USP Potassium Sodium Tartrate RS (September 1, 2005)
USP Potassium Sorbate (AS)
USP Propionic Acid (AS)
USP Ramipril Related Compound D RS (November 1, 2005)
USP Residual Solvent Class 2—Chloroform RS (May 1, 2005)
USP Residual Solvent Class 2—Cyclohexane RS (May 1, 2005)
USP Residual Solvent Class 2—1,2-Dichloroethene RS (March 1, 2005)
USP Residual Solvent Class 2—1,2-Dimethoxyethane RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS (May 1, 2005)
USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS (May 1, 2005)
USP Residual Solvent Class 2—2-Ethoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Formamide RS (May 1, 2005)

USP Residual Solvent Class 2—Hexane RS (November 1, 2005)
USP Residual Solvent Class 2—2-Methoxyethanol RS (May 1, 2005)
USP Residual Solvent Class 2—Methylbutylketone RS (May 1, 2005)
USP Residual Solvent Class 2—*N*-Methylpyrrolidone RS (May 1, 2005)
USP Residual Solvent Class 2—Mixture A RS (May 1, 2005)
USP Residual Solvent Class 2—Mixture C RS (May 1, 2005)
USP Residual Solvent Class 2—Nitromethane RS (May 1, 2005)
USP Residual Solvent Class 2—Pyridine RS (May 1, 2005)
USP Residual Solvent Class 2—Sulfolane RS (May 1, 2005)
USP Residual Solvent Class 2—Tetralin RS (May 1, 2005)
USP Residual Solvent Class 2—Trichloroethylene RS (May 1, 2005)
USP Sevoflurane Related Compound B RS (July 1, 2005)
USP Sevoflurane Related Compound C RS (July 1, 2005)
USP β-Sitosterol RS (September 1, 2005)
USP Sodium Acetate (AS)
USP Sodium Bicarbonate (AS)
USP Sodium Carbonate Anhydrous (AS)
USP Sodium Chloride (AS)
USP Sodium Citrate (AS)
USP Sodium Metabisulfite (AS)
USP Sodium Nitrite (AS)
USP Sodium Sulfate Anhydrous (AS)
USP Sodium Thiosulfate (AS)
USP Sorbic Acid (AS)
USP Sumatriptan Succinate Related Impurities RS (November 1, 2005)
USP Tannic Acid RS (September 1, 2005)
USP Tartaric Acid RS (September 1, 2005)
USP Terbutaline Related Compound A RS (September 1, 2005)
USP Thymol RS (November 1, 2005)
USP Tilmicosin RS (November 1, 2005)
USP Titanium Dioxide (AS)
USP Tolcapone RS (July 1, 2005)
USP Tolcapone Related Compound B RS (September 1, 2005)
USP Trenbolone CIII RS (November 1, 2005)
USP Trenbolone Acetate CIII RS (November 1, 2005)
USP Trolamine RS (November 1, 2005)
USP Tylosin Tartrate RS (September 1, 2005)
USP Urea RS (September 1, 2005)
USP Zinc Oxide (AS)
USP Zinc Sulfate (AS)

The official dates of any *USP 28* or *NF 23* 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 Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Berberine Chloride RS
USP Budesonide RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Cetrimonium Bromide RS
USP Clopidogrel Bisulfate RS
USP Clopidogrel Bisulfate Related Compound A RS
USP Clopidogrel Bisulfate Related Compound B RS
USP Clopidogrel Bisulfate Related Compound C RS
USP Copolymer Polypropylene RS
USP Cytosine RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluticasone Propionate Resolution Mixture RS
USP Fluticasone Propionate System Suitability Mixture RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Hydrastine Hydrochloride RS
USP Insulin Lispro RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Mecamylamine Related Compound A RS
USP Mefloquine Hydrochloride RS
USP Mefloquine Related Compound A RS
USP Menotropins RS
USP Methyldopa-glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Related Compound A RS
USP Naratriptan Related Compound B RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Norphenylephrine Hydrochloride RS
USP Ondansetron RS
USP Paricalcitol Solution RS
USP Maritime Pine Extract RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Polyoxyl 20 Cetostearyl Ether RS
USP Polyoxyl 20 Stearyl Ether RS
USP Posterior Pituitary RS
USP Potassium Perchlorate RS
USP Proinsulin (Beef) RS
USP Proinsulin (Pork) RS
USP Propofol for System Suitability RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Ropivacaine Hydrochloride RS
USP Ropivacaine Related Compound A RS
USP Ropivacaine Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Sulfaquinoxaline Related Compound A RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tiagabine Related Compound A RS
USP Racemic Tiagabine Hydrochloride Mixture RS
USP Tiagabine Hydrochloride RS
USP Tinidazole Related Compound B RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS

USP Vasopressin RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS

NOTICE OF POSTPONEMENT

Fexofenadine Hydrochloride and *Fexofenadine Hydrochloride Capsules*

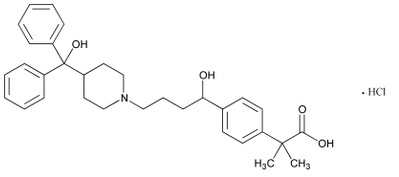
USP has **postponed indefinitely** the official dates of the *Fexofenadine Hydrochloride* and *Fexofenadine Hydrochloride Capsules* monographs, which were published in the *First Supplement* to *USP 28–NF 23* on pages 3227 and 3228 respectively. These monographs were originally slated to become official on April 1, 2005. The postponements are to provide additional time to further evaluate some of the tests, procedures, and acceptance criteria provided in the proposed monographs.

The Pharmaceutical Analysis 1 Expert Committee is presently reviewing comments received concerning these monographs. The USP intends to publish, if necessary, additional proposed revisions in a future issue of *Pharmacopeial Forum* for further public review and comment. USP proposes that these monograph revisions go forward to official text once the public comments have been considered.

Should you have any questions, please contact Karen A. Russo, Ph.D., Associate Director, Noncomplex Actives and Excipients, and liaison to the Pharmaceutical Analysis 1 Expert Committee (301-816-8379 or kar@usp.org).

Change to read:

•Fexofenadine Hydrochloride



$C_{32}H_{39}NO_4 \cdot HCl$ 538.12

Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl-, hydrochloride, (±)-.

(±)-*p*-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]butyl]-α-methylhydratropic acid, hydrochloride [*138452-21-8*].

» Fexofenadine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{32}H_{39}NO_4 \cdot HCl$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Fexofenadine Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

C: *Differential scanning calorimetry* ⟨891⟩—Accurately weigh 2 to 6 mg of Fexofenadine Hydrochloride into an aluminum pan, and crimp the pan, using a suitable sample press. Analyze the sample from 25° to 225° at 10° per minute. The sample exhibits a single endotherm between 193° and 199°. [NOTE—The pan can be sealed hermetically, provided a pinhole is punched into the lid so that the sample can degas during heating.]

Water, *Method Ic* ⟨921⟩: not more than 0.5%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Specific surface area, *Method II* ⟨846⟩**—**Outgas a portion of Fexofenadine Hydrochloride, 0.2 to 0.5 g, using helium flow for 1 hour at 100° or vacuum for 1 hour at 100°. Test the sample, using gas sorption: between 2.5 and 5.0 m^2 per g is found.

Limit of fexofenadine related compound B—

Ammonium acetate buffer solution—Add 2.3 mL of glacial acetic acid to 2000 mL of water. Adjust with 6 N ammonium hydroxide to a pH of 4.0 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of *Ammonium acetate buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Add about 1.2 mg of USP Fexofenadine Related Compound B RS, accurately weighed, to a 5-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix. Transfer 2.0 mL of the solution so obtained into a 100-mL volumetric flask; add about 25 mg of USP Fexofenadine Hydrochloride RS, accurately weighed; dilute with *Mobile phase* to volume; and mix.

Standard solution—Dilute the *System suitability solution* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 2.5 µg of USP Fexofenadine Hydrochloride RS per mL.

Test solution—Dissolve an accurately weighed quantity of Fexofenadine Hydrochloride in *Mobile phase* to obtain a solution having a concentration of about 0.25 mg per mL.

NOTICE OF POSTPONEMENT (*continued*)

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 L45. The column is maintained at room temperature. 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 retention time for fexofenadine is between 15 and 23 minutes; the relative retention times are about 0.7 for fexofenadine related compound B and 1.0 for fexofenadine; and the resolution, *R,* between fexofenadine and fexofenadine related compound B is not less than 3.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of fexofenadine related compound B in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100/0.8(c_S/c_T)(r_U/r_S),$$

in which 0.8 is the relative response factor for fexofenadine related compound B relative to fexofenadine; c_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* c_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response for fexofenadine related compound B obtained from the *Test solution;* and r_S is the peak response for fexofenadine obtained from the *Standard solution:* not more than 0.1% is found.

Related compounds—

Phosphate–perchlorate buffer, Diluting solution, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Reference solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* the *Standard solution,* the *Reference solution,* and *Mobile phase* (used as the blank) into the chromatograph; record the chromatograms; and measure the peak areas, excluding the peaks corresponding to those obtained from the *Mobile phase*. Calculate the percentage of fexofenadine related compound A in the portion of Fexofenadine 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 Fexofenadine Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* and r_U and r_S are the peak responses for fexofenadine related compound A obtained from the *Test solution* and the *Standard solution,* respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula:

$$(100/1.1)(C_S/C_T)(r_U/r_S),$$

in which C_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response of the decarboxylated degradant obtained from the *Test solution;* r_S is the peak response of fexofenadine obtained from the *Standard solution;* and 1.1 is the relative response factor for the decarboxylated degradant relative to fexofenadine. Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride 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 fexofenadine in the *Reference solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_i is the peak response for any other impurity obtained from the *Test solution;* and r_S is the peak response of fexofenadine obtained from the *Reference solution:* not more than 0.18% of fexofenadine related compound A is found; not more than 0.15% of decarboxylated degradant is found; not more than 0.1% of any other unknown impurity is found; and not more than 0.30% of total impurities is found.

Content of chloride—Dissolve about 300 mg of Fexofenadine Hydrochloride, accurately weighed, in 50 mL of methanol. Titrate with 0.1 N silver nitrate VS, and determine the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N silver nitrate VS is equivalent to 3.545 mg of chloride: not less than 6.45% and not more than 6.75% of chloride is found, calculated on an anhydrous basis.

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 2.0.

Diluting solution—Prepare a mixture of acetonitrile and *Phosphate–perchlorate buffer* (50 : 50).

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate–perchlorate buffer* and acetonitrile (65 : 35). Add 3 mL of triethylamine per L, and mix. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Prepare a solution of USP Fexofenadine Hydrochloride RS and USP Fexofenadine Related Compound A RS in *Mobile phase* having known concentrations of about 0.06 mg per mL and 0.005 mg per mL, respectively.

Assay stock preparation—Transfer about 50 mg of Fexofenadine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with *Diluting solution* to volume to obtain a solution having a concentration of about 1.0 mg of fexofenadine hydrochloride per mL.

Assay preparation—Transfer 3.0 mL of the *Assay stock preparation* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution having a concentration of about 0.06 mg per mL.

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 L11. The column is maintained at room temperature. 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 fexofenadine and fexofenadine related compound A is not less than 10; the tailing factor is not more than 2.0; and the relative standard deviations for replicate injections determined from fexofenadine and fexofenadine related compound A are not more than 2.0% and 3.0%, respectively.

NOTICE OF POSTPONEMENT (*continued*)

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 $C_{32}H_{39}NO_4 \cdot HCl$ in the portion of Fexofenadine Hydrochloride 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 for fexofenadine obtained from the *Assay preparation* and the *Standard preparation,* respectively.●3

●(Postponed indefinitely)●3

Change to read:

●Fexofenadine Hydrochloride Capsules

» Fexofenadine Hydrochloride Capsules contain not less than 93.0 percent and not more than 105.0 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. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A 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°.

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 0.3 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⟩).

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 Related Compound A RS.] Dissolve an accurately weighed quantity of USP Fexofenadine 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 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 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.

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.

Related compounds—

Phosphate–perchlorate buffer, Diluting solution, Mobile phase, 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.*

Reference solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

NOTICE OF POSTPONEMENT (*continued*)

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 related compound A in the portion of Capsules 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 Fexofenadine Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* and r_U and r_S are the peak responses of fexofenadine related compound A obtained from the *Test solution* and the *Standard solution,* respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula:

$$(100/1.1)(C_S / C_T)(r_U / r_S),$$

in which 1.1 is the relative response factor for the decarboxylated degradant relative to fexofenadine; C_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response of the decarboxylated degradant obtained from the *Test solution;* and r_S is the peak response of fexofenadine obtained from the *Standard solution*. Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100(C_R / C_T)(r_U / r_R),$$

in which C_R is the concentration, in mg per mL, of fexofenadine in the *Reference solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response for any other impurity obtained from the *Test solution;* and r_R is the peak response of fexofenadine obtained from the *Reference solution.* Not more than 0.3% of fexofenadine related compound A, not more than 0.2% of decarboxylated degradant, and less than 0.1% of any other unknown impurity is found; not more than 0.2% total other unknown impurities, and not more than 0.5% of total impurities is found.

Assay—

Phosphate–perchlorate buffer, Diluting solution, Mobile phase, 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.●3

●(Postponed indefinitely)●3

Interim Revision Announcement

NOTICE OF POSTPONEMENT

Helium, Nitrous Oxide, Nitrogen, and *Nitrogen 97 Percent*

USP has **postponed indefinitely** the official dates of the revisions to the *Helium, Nitrous Oxide, Nitrogen,* and *Nitrogen 97 Percent* monographs, which were published in the *First Supplement* to *USP 28–NF 23* on pages 3245, 3264, 3359, and 3359, respectively. These revisions were originally slated to become official on April 1, 2005. The postponements are due to the unavailability of the following USP Reference Standards:

(1) USP Air–Helium RS
(2) USP Nitrogen RS
(3) USP Oxygen–Helium RS
(4) USP Nitrous Oxide RS
(5) USP Nitrogen 97 Percent RS

These postponements are in accordance with the Rules and Procedures of the Council of Experts that state:

> *"Where a new reference standard is required in a new monograph or in a revision of an existing monograph but is not yet available, the official date of any portion of the monograph utilizing such reference standard shall be postponed until such reference standard is available. During the period of such unavailability, the Chairperson of the Council of Experts shall publish the name of such reference standards and indicate that it is not yet available. Subsequently, the availability of the reference standards shall be announced and the effective date of the postponed portion(s) of the monograph shall be announced."*

Should you have any questions, please contact Khakashan Zaidi, Ph.D., Scientist, General Policies and Requirements Division and liaison to the Aerosols Expert Committee (301-816-8379 or kxz@usp.org).

Helium

Change to read:

•**USP Reference standards** ⟨11⟩—*USP Air–Helium RS.*•

•(Postponed indefinitely)•

Change to read:

Assay—Introduce a specimen of Helium into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of nitrogen and oxygen from Helium, although the nitrogen and oxygen may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •USP Air–Helium RS,• and indicates not more than 1.0% of air when compared to the peak response of the •USP Air–Helium RS,• and not less than 99.0%, by volume, of He.

•(Postponed indefinitely)•

Nitrous Oxide

Change to read:

•**USP Reference standards** ⟨11⟩—*USP Air–Helium RS. USP Nitrous Oxide RS.*•

•(Postponed indefinitely)•

NOTICE OF POSTPONEMENT *(continued)*

Change to read:

Identification—

A: With the container temperatures the same and maintained between 15° and 25°, concomitantly read the pressure of the Nitrous Oxide container and of a container of •USP Nitrous Oxide RS.•$_{3}$ [NOTE—Do not use the •USP Nitrous Oxide RS•$_{3}$ if it has been depleted to less than half of its full capacity.] The pressure of the Nitrous Oxide container is within 50 psi of that of the •USP Nitrous Oxide RS.•$_{3}$

B: Pass 100 ± 5 mL released from the vapor phase of the contents of the Nitrous Oxide container through a carbon dioxide detector tube at the rate specified for the tube: no color change is observed *(distinction from carbon dioxide).*

C: Collect about 100 mL of the gas under test in a 100-mL tube fitted at the top with a stopcock. Open the stopcock, and quickly add a freshly prepared solution of 500 mg of pyrogallol in 2 mL of water and a freshly prepared solution of 12 g of potassium hydroxide in 8 mL of water. Immediately close the stopcock, and mix: the gas is not absorbed, and the solution does not become brown *(distinction from oxygen).*

•D: Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrous Oxide RS and a sample of Nitrous Oxide into the gas chromatograph. The retention time of the major peak in the chromatogram of the Nitrous Oxide sample corresponds to that in the chromatogram of the USP Nitrous Oxide RS.•$_{3}$

•(Postponed indefinitely)•$_{3}$

Change to read:

Assay—Introduce a specimen of Nitrous Oxide taken from the liquid phase, as directed in the test for *Nitrogen dioxide,* into a gas chromatograph by means of a gas-sampling valve. Select the operating conditions of the gas chromatograph such that the peak response resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of N_2 and O_2 from N_2O, although the N_2 and O_2 may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •USP Air–Helium RS,•$_{3}$ and is equivalent to not more than 1.0% of air when compared to the peak response of the •USP Air–Helium RS,•$_{3}$ indicating not less than 99.0%, by volume, of N_2O.

•(Postponed indefinitely)•$_{3}$

Nitrogen

Change to read:

•USP Reference standards ⟨11⟩*—USP Nitrogen RS. USP Oxygen–Helium RS.*•$_{3}$

•(Postponed indefinitely)•$_{3}$

Change to read:

Identification—•Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrogen RS and the nitrogen sample into the gas chromatograph. The retention time of the major peak in the chromatogram of the nitrogen sample corresponds to that in the chromatogram of the USP Nitrogen RS.•$_{3}$

•(Postponed indefinitely)•$_{3}$

Change to read:

Assay—Introduce a specimen of Nitrogen into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 3 m in length and 4 mm in inside diameter and is packed with a molecular sieve prepared from a synthetic alkali-metal aluminosilicate capable of absorbing molecules having diameters of up to 0.5 nm, which permit complete separation of oxygen from nitrogen. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •the USP Oxygen–Helium RS,•$_{3}$ and is equivalent to not more than 1.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•$_{3}$ indicating not less than 99.0%, by volume, of N_2.

•(Postponed indefinitely)•$_{3}$

Nitrogen 97 Percent

Change to read:

•USP Reference standards ⟨11⟩*—USP Nitrogen 97 Percent RS. USP Oxygen–Helium RS.*•$_{3}$

•(Postponed indefinitely)•$_{3}$

Change to read:

Identification—•Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrogen 97 Percent RS and a sample of Nitrogen 97 Percent into the gas chromatograph. The retention time of the major peak in the chromatogram of the test sample corresponds to that in the chromatogram of the USP Nitrogen 97 Percent RS.•$_{3}$

•(Postponed indefinitely)•$_{3}$

Change to read:

Assay—Proceed as directed in the *Assay* under *Nitrogen.* The peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •the USP Oxygen–Helium RS•$_{3}$ and is equivalent to not more than 3.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•$_{3}$ indicating not less than 97.0%, by volume, of N_2.

•(Postponed indefinitely)•$_{3}$

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MONOGRAPHS (USP)

Butabarbital Sodium Tablets

Change to read:

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

•*Acid–methanol mixture*—Prepare a mixture of methanol and 1 N hydrochloric acid (9 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Butabarbital RS in *Acid–methanol mixture* to obtain a solution having a known concentration of about 0.45 mg per mL.•

Test preparation—Transfer 1 finely powdered Tablet to a 25-mL volumetric flask, •add *Acid–methanol mixture* to volume, and mix. Filter, discarding the first 5 mL of the filtrate, and dilute the subsequent filtrate quantitatively and stepwise if necessary, with *Acid–methanol mixture* to obtain a solution containing 0.5 to 0.6 mg of butabarbital sodium per mL.•

Procedure—•Transfer 2.0 mL each of the *Standard preparation* and the *Test preparation* to separate 100-mL volumetric flasks, and transfer 2.0 mL of *Acid–methanol mixture* to a third volumetric flask to provide a blank. Dilute each flask with pH 9.6 alkaline borate buffer (see under *Solutions* in the section *Reagents, Indicators, and Solutions*), and mix. Concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 240 nm, with a suitable spectrophotometer, using the blank to set the instrument.• Calculate the quantity, in mg, of $C_{10}H_{15}N_2NaO_3$ in the Tablet •taken• by the formula:

$$•(234.23/212.25)/(TC/D)(A_U/A_S)•$$

in which 234.23 and 212.25 are the molecular weights of butabarbital sodium and butabarbital, respectively; T is the labeled quantity, in mg, of butabarbital sodium in the Tablet; C is the concentration, in •mg• per mL, of USP Butabarbital RS in the *Standard preparation; D* is the concentration, in •mg• per mL, of butabarbital sodium in the *Test preparation,* based upon the labeled quantity per Tablet and the extent of dilution; and A_U and A_S are the absorbances of the solutions from the *Test preparation* and the *Standard preparation,* respectively.

Chondroitin Sulfate Sodium 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. •Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis.•

Glucosamine and Chondroitin Sulfate Sodium 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. •Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis.•

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.▲*USP28*]

TEST 1—

Medium: 0.01 N hydrochloric acid containing 0.2% sodium lauryl 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⟩).

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 *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.

•TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus, Time, Standard solution, and *Test solution*—Proceed as directed for *Test 1*. [NOTE—Filter the *Standard solution* in a manner identical to the *Test solution*.]

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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 and acetonitrile (65 : 35) with 0.5 mL of phosphoric acid per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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 5-µm packing L10. The column temperature is maintained at 30°. 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 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 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.●3

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

▲NOTE—Do not use paddle stirrers with synthetic coating.▲*USP28*

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 *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.

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MONOGRAPHS (NF)

Ferric Oxide

Change to read:

Acid-insoluble substances—Digest 2.0 g in 25 mL of hydrochloric acid by boiling for 20 minutes. Add 100 mL of hot water, and filter quantitatively through a tared filtering crucible, with the aid of hot wash water until the filtrate tests negative for chloride. Dry the crucible and contents at 105° for 1 hour: the residue weighs not more than ●6 mg (0.3%).●3

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Add the following:

●**USP Agnuside RS**—This material is hygroscopic. Keep container tightly closed. Protect from light. Store in a desiccator.●3

Change to read:

USP Bupropion Hydrochloride Related Compound B RS [2-(*tert*-butylamino)-3′-bromopropiophenone hydrochloride**]** ($C_{13}H_{18}BrNO \cdot HCl$ ✧ 320.66)—Do not dry. ●Keep container tightly closed. Protect from light. Store in a refrigerator.●3

Change to read:

USP Clonazepam RS—●Do not dry.●3 Keep container tightly closed. Protect from light.

Change to read:

USP Flurazepam Related Compound C RS [5-chloro-2-(2-diethylaminoethyl(amino)-2′-fluorobenzophenone hydrochloride] ($C_{19}H_{22}ClFN_2O \cdot HCl$ ✧ 385.31)—•Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$

Change to read:

■**USP Fluvoxamine Maleate RS**—•Dry portion at 80° for 2 hours before using. Keep container tightly closed. Protect from light.•$_3$■1S *(USP28)*

Change to read:

USP Indinavir •$_{•3}$ **System Suitability RS**—•Do not dry. Keep container tightly closed.•$_3$

Change to read:

USP Liothyronine RS—Do not dry before using. •Correct for moisture, determined by drying a separate portion in vacuum at 60° for 3 hours.•$_3$ Keep container tightly closed. Protect from light. •Store in a refrigerator.•$_3$

Change to read:

USP Maltose Monohydrate RS—•Do not dry. Keep container tightly closed.•$_3$

Change to read:

USP Octisalate RS [octyl salicylate]—•Do not dry. Keep container tightly closed.•$_3$

Delete the following:

•**USP Paroxetine Related Compound D RS** [*cis*-paroxetine hydrochloride]—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$

Change to read:

USP Propylparaben RS—•Do not dry.•$_3$ Keep container tightly closed.

Change to read:

USP Quercetin RS—•Do not dry. This is the dihydrate form. Keep container tightly closed. Protect from light. Store in a freezer.•$_3$

Change to read:

USP Ramipril Related Compound D RS [ethyl (2*S*)2-[(3*S*,5a*S*,8a*S*, 9*aS*)-3-methyl-1,4-dioxodecahydro-1*H*-cyclopenta[*e*]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenyl-butanoate] •**Ramipril Diketopiperazine**•$_3$ ($C_{23}H_{30}N_2O_4$ ✧ 398.50)—Do not dry. Keep container tightly closed. •Protect from light. Store in a refrigerator.•$_3$

Change to read:

USP Sodium Fluoride RS—•Do not dry.•$_3$ Keep container tightly closed.

Change to read:

▲**USP Sumatriptan Succinate Related Impurities RS** [Mixture of sumatriptan succinate, [3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide maleate salt, sumatriptan succinate related compound C, [3-[2-(dimethylamino-*N*-oxide)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide, and [3-[2-(aminoethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide]—•Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$▲*USP28*

Change to read:

USP Tilmicosin RS—•Allow vial to reach room temperature before opening. Open and allow to equilibrate for 30 minutes with ambient humidity before weighing for analysis. Determine water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$

Change to read:

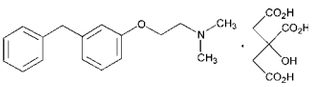
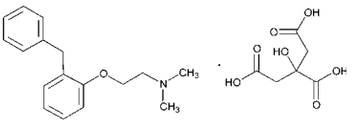
USP Trenbolone RS—•Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$

Change to read:

USP Trenbolone Acetate RS—•Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_3$

ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
270	*Bisoprolol Fumarate and Hydrochlorothiazide Tablets*	*Assay*	Line 2 under *Diluent:* Change "of water" to: a mixture of water and acetonitrile (1:1). *Solution A:* Change "Filter and degas a portion of the *Diluent.*" to: Mix 10 mL of 1 M dibutylammonium phosphate with 1000 mL of water.
		Identification A	Line 2 under *Developing solvent system:* Change "7.7 M" to: 14.5 M
		Dissolution	Line 2 under *Mobile phase:* Change "(4:1)." to: (1:4).
688	*Dolasetron Mesylate*	*Related compounds*	Line 3, column 2 of the gradient table: Change "250" to: 0
905	*Glucagon*	*Assay*	Line 5 under *Incubation buffer:* Change "1% bovine serum albumin." to: 1% bovine serum albumin (BSA).
			Line 2 under *Negative control solution:* Change "0.5% bis(trimethylsilyl)acetamide (BSA)" to: 0.5% BSA
1465	*Papain*	*Assay*	Line 2 under *Buffer solution:* Change "anhydrous dibasic phosphate" to: anhydrous dibasic sodium phosphate
1547	*Phenyltoloxamine Citrate*	*Chemical structure*	Change  to: 
1932	*Tilmicosin Injection*	*Assay*	Line 6 under *Procedure:* Change "$0.6(CP/V)(r_1/r_s)$" to: $0.6(CP/V)(r_1/r_S)$ and on line 12 under *Procedure:* Change "and r_s is the sum of the responses of the tilmicosin *trans*-isomers and tilmicosin *cis*-isomers obtained from the *Standard preparation.*" to: and r_S is the peak area response for the relevant (*trans* or *cis*) tilmicosin isomers obtained from the *Standard preparation.*

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ERRATA *(Continued)*

Page	Title	Section	Description
2505	⟨905⟩ *Uniformity of Dosage Units*	*Criteria*	Under *Transdermal Systems and Inhalations Packaged in Premetered Dosage Units, Limit B*, re-insert text to the list. List should read as follows: (1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.* (2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100". (3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".
2513	⟨941⟩ *X-Ray Diffraction*	*Fundamental Principles*	Line 12: Change "and is the angle" to: and θ is the angle
		Test Preparation	Line 10 of last paragraph: Change "values for 2 that" to: values for 2θ that Line 13: Change "(2 values" to: (2θ values Line 16–17: Change "the 2 region" to: the 2θ region
3070	*Saccharin*	*Toluenesulfonamides*	Line 3 under *Chromatographic system:* Change "13.2-mm × 8-m glass column" to: 3.2-mm × 1.8-m glass column
Supplement 1			
3239	*Glimepiride*	*Water*	Add to the end of the test: The water content is not more than 0.5%.

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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24*; and

■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*, ■2S (*USP 28*) indicates that the proposed revision is slated for the *Second Supplement to USP 28*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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 28* page 1, page 3208 of the *First Supplement,* and page 1571 of *PF* 30(5) [Sept.–Oct. 2004]. In the *Storage Temperature and Humidity* section, it is proposed to add a definition of *Controlled Cold Temperature* that will allow calculation of the mean kinetic temperature (MKT) at the cold temperature range in consideration of the storage, shipping, and distribution of pharmaceutical articles. A sample calculation of MKT is presented in general chapter *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩. The definition for *Controlled Cold Temperature* becomes an overarching definition that envelops the cold temperature definition, creating a continuum of temperature that allows excursions of temperature experienced during storage, shipping, and distribution.

(PSD: C. Okeke) RTS—42329-1

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⟩).

Although 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 *(USP29)*

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 semisynthetics 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

In-Process Revision

principles defined and the requirements specified in *Organic Volatile Impurities* ⟨467⟩, using the general methods presented therein or other suitable methods. [NOTE—*Residual Solvents* to become official January 1, 2007.]■2S (*USP28*)

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 use of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures used. 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 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 ensuring 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 fewer 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 fewer 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. ■Results are calculated on an "as-is" basis unless otherwise specified in the monograph.■1S (*USP28*) 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 $800 \pm 25^{\circ}$ 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, either of 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 $25^{\circ}/25^{\circ}$, 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 compli-

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ance with good manufacturing practices generally, are developed and followed to ensure 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 procedure specified in the *Assay,* the average of all of the individual *Content Uniformity* determinations may be used as the *Assay* value.

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.

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 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 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 packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging used 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 used 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.

■**Poison Prevention Packaging Act—**This act (see the Website, www.cpsc.gov/businfo/pppa.html) requires special packaging of most human oral prescription drugs, oral controlled drugs, certain nonoral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR § 1700.14).

The immediate packaging of substances regulated under the PPPA must comply with the special packaging standards (16 CFR § 1700.15 and 16 CFR § 1700.20). The PPPA regulations for special packaging apply to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Manufacturers and packagers of bulk-packaged prescription drugs do not have to use special packaging if the drug will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in nonchild-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. § 1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in nonchild-resistant packaging as long as popular-size, special packages are also supplied. The nonchild-resistant package requires special labeling (18 CFR § 1700.5).

Various types of child-resistant packages are covered in ASTM International Standard D-3475, Standard Classification of Child-Resistant Packaging. Examples are included as an aid in the understanding and comprehension of each type of classification.■2S (*USP28*)

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 *Pharmaceutical Stability* ⟨1150⟩). 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.

■*Controlled Cold Temperature*—This temperature is defined as the temperature maintained thermostatically between 2° and 8° (36° and 46 °F), that allows for excursions in temperature between 0° and 15° (32° and 59 °F) that may be experienced during storage, shipping, and distribution such that the allowable calculated MKT is not more than 8° (46 °F). Transient spikes up to 25° (77 °F)

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may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours for cold storage.■1S (*USP29*)

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 *Pharmaceutical Stability* ⟨1150⟩.)

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—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.

■**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 (*USP29*)

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 1 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 Botanical-Containing Products*—The label of an herb or other botanical intended for use as a dietary supplement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product."▲*USP28*

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 or 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) 1 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 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's 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 test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

■**Guidelines for Packaging and Storage Statements in *USP–NF* Monographs—**In order to provide users of the *USP–NF* with proper guidance on how to package and store compendial articles, every monograph in the *USP–NF* is required to have a packaging and storage specification.

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For those instances where, for some reason, storage information is not yet found in the *Packaging and storage* specification of a monograph, the section *Storage Under Non-Specific Conditions* is included in the *General Notices* as interim guidance. The *Storage Under Nonspecific Conditions* statement is not meant to substitute for the inclusion of proper, specific storage information in the *Packaging and storage* statement of any monograph.

For the packaging portion of the statement, the choice of containers is given in the *General Notices* and includes *Light-Resistant Container, Well-Closed Container, Tight Container, Hermetic Container, Single-Unit Container, Single-Dose Container, Unit-Dose Container,* and *Unit-of-Use Container.* For most preparations, the choice is determined by the container in which it is to be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc). For active pharmaceutical ingredients (APIs), the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate default. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.

For the storage portion of the statement, the choice of storage temperatures presented in the *General Notices* includes *Freezer, Cold, Cool,* ■*Controlled Cold Temperature,* ■1S (*USP29*) *Room Temperature, Controlled Room Temperature, Warm, Excessive Heat,* and *Protection from Freezing.* The definition of a dry place is provided if protection from humidity is important.

For most preparations, the choice is determined by the experimentally determined stability of the preparation and may include any of the previously stated storage conditions as determined by the manufacturer. For APIs that are expected to be retested before incorporation into a preparation, a more general and nonrestrictive condition may be desired. In this case, the specification "room temperature" (the temperature prevailing in a working area) should suffice. The use of the permissive room temperature condition reflects the stability of an article over a wide temperature range. For excipients, the phrase "No storage requirements specified" in the *Packaging and storage* statement of the monograph would be appropriate.

Because most APIs in the *USP–NF* have associated Reference Standards, special efforts should be considered to ensure that the Reference Standards' storage conditions correspond to the conditions indicated in the *USP–NF* monographs.

The Packaging, Storage, and Distribution Expert Committee may review questionable *Packaging and storage* statements on a case-by-case basis. In cases where the *Packaging and storage* statements are incomplete, the monographs would move forward to publication while the *Packaging and storage* statements are temporarily deferred.■2S (*USP28*)

MONOGRAPHS (USP)

BRIEFING

Acetylcysteine, *USP 28* page 46. It is proposed to introduce a new USP Reference Standard, USP L-Phenylalanine RS, to replace DL-phenylalanine used in the *Internal standard solution* of the *Assay.*

(PA2: C. Anthony) RTS—42459-1

Change to read:

USP Reference standards ⟨11⟩—*USP Acetylcysteine RS.*

■*USP L-Phenylalanine RS.*■1S *(USP29)*

Change to read:

Assay—

Mobile phase—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, pass through a membrane filter having a 0.45-µm porosity, and degas. Adjust with phosphoric acid to a pH of 3.0.

Internal standard solution—Dissolve about 1 g of ~~DL-phenylalanine~~

■USP L-Phenylalanine RS■1S *(USP29)*
in 200 mL of freshly prepared sodium metabisulfite solution (1 in 2000).

Standard preparation—Dissolve an accurately weighed quantity of USP Acetylcysteine RS in sodium metabisulfite solution (1 in 2000) to obtain a solution having a known concentration of about 10 mg per mL. Pipet 10.0 mL of this solution and 10.0 mL of *Internal standard solution* into a 200-mL volumetric flask, dilute with sodium metabisulfite solution (1 in 2000) to volume, and mix to obtain a *Standard preparation* having a known concentration of about 0.5 mg per mL of USP Acetylcysteine RS.

Assay preparation—Transfer about 1000 mg of Acetylcysteine, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with sodium metabisulfite solution (1 in 2000) to volume, and mix. Pipet 10.0 mL of this solution and 10.0 mL of *Internal standard solution* into a 200-mL volumetric flask, dilute with sodium metabisulfite solution (1 in 2000) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-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 standard deviation for replicate injections is not more than 2.0%; and the resolution, *R,* between acetylcysteine and DL-phenylalanine is not less than 6.

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 responses for the major peaks. The relative retention times are about 0.5 for acetylcysteine and 1.0 for ~~DL-phenylalanine.~~

■L-phenylalanine.■1S *(USP29)*
Calculate the quantity, in mg, of $C_5H_9NO_3S$ in the portion of Acetylcysteine taken by the formula:

$$2000C(R_U / R_S),$$

in which C is the concentration, in mg per mL, of USP Acetylcysteine RS in the *Standard preparation;* and R_U and R_S are the ratios of the peak response of acetylcysteine to that of ~~DL-phenylalanine~~

■L-phenylalanine■1S *(USP29)*
obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Albuterol Tablets, *USP 28* page 58 and page 40 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to revise the *Procedure* in the *Assay* by correcting the formula to indicate that one molecule of albuterol sulfate liberates two molecules of albuterol.

(PA1: K. Russo) RTS—42436-1

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

▲▲*USP29*
⟨711⟩—

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of $C_{13}H_{21}NO_3$ dissolved using the following method.

Mobile phase, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Procedure—

▲Proceed as directed for *Procedure for Capsules, Uncoated Tablets,* and *Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.▲*USP29*
Inject a suitable volume (about 100 µL) of ~~a portion of the solution under test,~~

▲the pooled sample,▲*USP29*

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previously filtered through a 0.45-µm nylon filter, into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{13}H_{21}NO_3$ dissolved by comparing this peak response with the major peak response similarly obtained on chromatographing the *Standard preparation* previously diluted, if necessary, with a mixture of water and methanol (6 : 4) to obtain a Standard solution having a known concentration of USP Albuterol Sulfate RS approximately corresponding to the concentration of the solution under test.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{13}H_{21}NO_3$ is dissolved in 30 minutes:

▲the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q,* is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

▲*USP29*

Change to read:

Assay—

1% Acetic acid—Transfer a 20-mL portion of glacial acetic acid to a suitable volumetric flask, and dilute with water to 2000 mL.

Mobile phase—Dissolve 1.13 g of sodium 1-hexanesulfonate in 1200 mL of water, add 12 mL of glacial acetic acid, and mix. Prepare a filtered and degassed mixture of this solution and methanol (6 : 4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12 mg of USP Albuterol Sulfate RS, accurately weighed, to a 100-mL volumetric flask. Add 60 mL of *1% Acetic acid,* sonicate for 5 minutes, dilute with methanol to volume, and mix. Pipet 25 mL of this solution into a 100-mL volumetric flask, dilute with a mixture of water and methanol (6 : 4) to volume, and mix.

Assay preparation—Transfer a number of whole Tablets, equivalent to about 50 mg of albuterol, to a 2000-mL volumetric flask. Add 1200 mL of *1% Acetic acid,* shake by mechanical means for 45 minutes, sonicate for 10 minutes, allow to cool to room temperature, dilute with methanol to volume, and mix. Pass through a suitable filter having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 276-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 preparation,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 800 theoretical plates; the tailing factor for the analyte peak 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 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 albuterol ($C_{13}H_{21}NO_3$) in the number of Tablets taken by the formula:

~~$2(239.32/576.71)200C(r_U/r_S)$,~~

~~in which 239.32 and 576.71 are the molecular weights of albuterol and albuterol sulfate, respectively; *C* is the concentration, in mg per mL, of USP Albuterol Sulfate 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.~~

■$2000C(r_U/r_S)(2)(239.31/576.70)$,

in which 2000 is the volume, in mL, of the *Assay preparation; C* is the concentration, in mg per mL, of USP Albuterol Sulfate RS in the *Standard preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; 2 is the number of molecules of albuterol released from each molecule of albuterol sulfate; and 239.31 and 576.70 are the molecular weights of albuterol and albuterol sulfate, respectively.■1S (*USP29*)

BRIEFING

Anticoagulant Citrate Dextrose Solution, *USP 28* page 165 and page 1583 of *PF* 30(5) [Sep.–Oct. 2004]—See briefing under *Anticoagulant Sodium Citrate Solution*.

(BBP: R. Tirumalai; D. Bempong) RTS—42196-2

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Change to read:

USP Reference standards ⟨11⟩—

■*USP Citric Acid RS.*■1S *(USP29)*
USP Endotoxin RS.

(Official April 1, 2009)

Change to read:

Assay for total citrate ~~—Proceed as directed in the *Assay for total citrate* under *Anticoagulant Citrate Phosphate Dextrose Solution*. Report total citrate per L of sample (as citric acid, anhydrous).~~

■*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Pipet 5 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under general chapter ⟨345⟩.

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of Solution taken by the formula:

$$0.001(192.12/189.10)C_S D(r_U / r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.■1S *(USP29)*

(Official April 1, 2009)

Change to read:

Assay for dextrose—Determine the angular rotation of the Solution in a ~~200-mm tube, using sodium light at 25°. The observed rotation in degrees, multiplied by 1.0425, represents the weight of $C_6H_{12}O_6 \cdot H_2O$ in 100 mL of the solution.~~ ■suitable polarimeter tube (see *Optical Rotation* ⟨781⟩). Where the Solution is labeled to contain anhydrous dextrose, calculate the percentage (g per 100 mL) of $C_6H_{12}O_6$ in the portion of Solution taken by the formula:

$$(100/52.9)AR,$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; *A* is 100 mm divided by the length of the polarimeter tube, in mm; and *R* is the observed rotation, in degrees. Where the Solution is labeled to contain dextrose monohydrate, calculate the percentage (g per 100 mL) of $C_6H_{12}O_6 \cdot H_2O$ in the portion of Solution taken by the formula:

$$(100/52.9)(198.17/180.16)AR,$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; *A* is 100 mm divided by the length of the polarimeter tube, in mm; and *R* is the observed rotation, in degrees.■2S *(USP28)*

BRIEFING

Anticoagulant Citrate Phosphate Dextrose Adenine Solution, *USP 28* page 166 —See briefing under *Anticoagulant Sodium Citrate Solution*.

(BBP: R. Tirumalai; D. Bempong) RTS—42196-4

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩—*USP Adenine RS.*

■*USP Citric Acid RS.*■1S (*USP29*)
USP Endotoxin RS.

(Official April 1, 2009)

Delete the following:

■~~**Assay for total citrate**—~~

~~*Standard preparations*—Dissolve a suitable quantity of citric acid, previously dried at 90° for 3 hours and accurately weighed, in water to obtain a solution having a known concentration of about 1.0 mg of anhydrous citric acid per mL. Further pipet quantities of 8, 9, 10, 11, and 12 mL of this stock standard into separate 100-mL volumetric flasks, dilute with water to volume, and mix.~~

~~*Assay preparation*—Pipet 5 mL of Solution into a 1000-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Pipet 1 mL of the *Assay preparation,* each *Standard preparation,* and water into separate test tubes. To each tube add 1.3 mL of pyridine, and mix by swirling. To one tube at a time add 5.7 mL of acetic anhydride, and mix, using a rotary vortex stirrer. Immediately place in a water bath maintained at 31 ± 1.0°, and allow the color to develop for 33 ± 1 minutes. Determine the absorbance against the reference blank in 1-cm cells at 425 nm, taking care to measure the absorbance of each solution at the same elapsed time from mixing. Calculate the total citrate content, in mg per mL, of the Solution taken by the formula:~~

~~$0.2C$,~~

~~in which C is the concentration, in µg per mL, of anhydrous citric acid read from the standard curve.~~■1S (*USP29*)

(Official April 1, 2009)

Delete the following:

■~~Assay for total phosphate [expressed as monobasic sodium phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$)]—~~

~~*Acid solution*—Dilute 75 mL of sulfuric acid to 200 mL with water.~~

~~*Ammonium molybdate solution*—Dissolve 25 g of ammonium molybdate in 300 mL of water, and add 200 mL of *Acid solution.*~~

~~*Standard preparation*—Dissolve about 0.44 g of monobasic potassium phosphate, previously dried at 105° for 4 hours and accurately weighed, in water to make 1000 mL, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.01 mg of phosphorus (P) per mL.~~

~~*Assay preparation*—Pipet 10 mL of Solution into a 500-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Pipet 5-, 10-, and 15-mL portions of the *Standard preparation* and 10 mL of the *Assay preparation* into separate 50-mL volumetric flasks. Treat the contents of each flask as follows. Add 2.5 mL of *Ammonium molybdate solution,* and mix. Add rapidly, and in order, 2.5 mL of hydroquinone solution (1 in 200) and 2.5 mL of sodium sulfite solution (1 in 10), both prepared fresh daily. Dilute with water to volume, mix, and allow to stand at room temperature for 30 ± 5 minutes. Determine the absorbances against water in 1-cm cells at 660 nm with a suitable spectrophotometer. Plot the absorbances against the mg of phosphorus in the portions of *Standard preparation* taken. Calculate the quantity, in mg, of $NaH_2PO_4 \cdot H_2O$ in each mL of the Solution taken by the formula:~~

~~$(137.99/30.9738)(5W)$,~~

~~in which 137.99 is the molecular weight of monobasic sodium phosphate monohydrate; 30.9738 is the atomic weight of phosphorus; and W is the weight, in mg, of P in the 10 mL of *Assay preparation* taken, read from the Standard curve.~~■1S (*USP29*)

(Official April 1, 2009)

Add the following:

■**Assay for total citrate and total phosphate**—

Mobile Phase, Standard Preparation 2, and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation for total citrate assay—Pipet 10 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under general chapter ⟨345⟩.

Assay preparation for total phosphate assay—Pipet 5 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Phosphate Assay* under general chapter ⟨345⟩.

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of Solution taken by the formula:

$$0.001(192.12/189.10)C_S D(r_U / r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 2; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation for total citrate assay* and *Standard Preparation 2,* respectively.

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Calculate the quantity, in mg, of phosphate, expressed as monobasic sodium phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), in the volume of Solution taken by the formula:

$$0.001(137.99/94.97)C_S D(r_U / r_S),$$

in which 137.99 is the molecular weight of monobasic sodium phosphate monohydrate; 94.97 is the molecular weight of phosphate (PO_4); C_S is the concentration, in µg per mL, of phosphate in *Standard Preparation 2; D* is the dilution factor; and r_U and r_S are the phosphate peak areas obtained from the *Assay preparation for total phosphate assay* and *Standard Preparation 2,* respectively.■1S (*USP29*)

(Official April 1, 2009)

BRIEFING

Anticoagulant Citrate Phosphate Dextrose Solution, *USP 28* page 165—See briefing under *Anticoagulant Sodium Citrate Solution*.

(BBP: R. Tirumalai; D. Bempong) RTS—42196-3

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩—

■*USP Citric Acid RS.*■1S (*USP29*)
USP Endotoxin RS.

(Official April 1, 2009)

Delete the following:

■~~**Assay for total citrate**~~

~~*Standard preparations*—Dissolve a suitable quantity of citric acid, previously dried at 90° for 3 hours and accurately weighed, in water to obtain a stock solution having a known concentration of about 1.0 mg of anhydrous citric acid per mL. Pipet aliquots of 8, 9, 10, 11, and 12 mL, respectively, of the stock solution into separate 100-mL volumetric flasks, dilute with water to volume, and mix.~~

~~*Assay preparation*—Pipet 10 mL of Solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into another 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Pipet 1 mL of the *Assay preparation,* each *Standard preparation,* and water into a suitable test tube. To each tube add 1.3 mL of pyridine, and mix by swirling. To one tube at a time add 5.7 mL of acetic anhydride, and mix, using a rotary vortex stirrer. Immediately place in a water bath maintained at 31 ± 1.0°, and allow the color to develop for 33 ± 1 minutes. Determine the absorbance against the reference blank in 2.5-cm cells at 425 nm, taking care to measure the absorbance of each solution at the same elapsed time from mixing. Plot the absorbances of the *Standard preparations* versus the concentrations, and draw the straight line best fitting the plotted points. From the graph so obtained, calculate the total citrate content, in mg per mL, of the Anticoagulant Citrate Phosphate Dextrose Solution taken by the formula:~~

~~$0.2C,$~~

~~in which *C* is the concentration, in µg per mL, of anhydrous citric acid read from the standard curve.~~ ■1S (*USP29*)

(Official April 1, 2009)

Delete the following:

■~~**Assay for total phosphate** [expressed as monobasic sodium phosphate, monohydrate ($NaH_2PO_4 \cdot H_2O$)]~~

~~*1,2,4-Aminonaphtholsulfonic acid solution*—Dissolve 0.5 g of 1,2,4-aminonaphtholsulfonic acid in about 150 mL of sodium metasulfite solution (3 in 20) in a 200-mL volumetric flask, warming if necessary. Add 5 mL of sodium sulfite solution (1 in 5), mix, and dilute with sodium metasulfite solution (3 in 20) to volume.~~

~~*Standard preparation*—Dissolve about 0.44 g of monobasic potassium phosphate, accurately weighed, in water to make 1000 mL, and mix. Pipet 25 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume so as to obtain a solution having a known concentration of about 0.11 mg per mL of monobasic potassium phosphate.~~

~~*Assay preparation*—Dilute 5.0 mL of Solution with water to 100 mL.~~

~~*Procedure*—Pipet 5 mL of *Standard preparation,* 5 mL of *Assay preparation,* and 5 mL of water, to provide a control, into separate 25-mL volumetric flasks. Treat the contents of each flask as follows. Add 10.0 mL of 1 N sulfuric acid, and mix. Add 2.0 mL of ammonium molybdate solution (1 in 40), and mix. Add 1.0 mL of *1,2,4-Aminonaphtholsulfonic acid solution,* dilute with water to volume, again mix, and allow to stand for 10 minutes at 20° to 25°. Determine the absorbances of the solutions from the *Standard preparation* and the *Assay preparation* against the reference solution in 1-cm cells at 660 nm, with a suitable spectrophotometer, taking care to measure the absorbance of each solution at the same elapsed time from mixing. Calculate the quantity, in mg, of monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$) in each mL of the Solution taken by the formula:~~

~~$20.28C(A_U/A_S),$~~

~~in which *C* is the concentration, in mg per mL, of KH_2PO_4 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.~~ ■1S (*USP29*)

(Official April 1, 2009)

Add the following:

■**Assay for total citrate and total phosphate**—

Mobile Phase, Standard Preparation 2, and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation for total citrate assay—Pipet 10 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under general chapter ⟨345⟩.

Assay preparation for total phosphate assay—Pipet 5 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Phosphate Assay* under general chapter ⟨345⟩.

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, and calculate the quantity, in mg, of anhydrous citric acid ($C_6H_8O_7$) in the volume of Solution taken by the formula:

$$0.001(192.12/189.10)C_S D(r_U / r_S),$$

in which 192.12 is the molecular weight of anhydrous citric acid; 189.10 is the molecular weight of citrate ($C_6H_5O_7$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 2; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation for total citrate assay* and *Standard Preparation 2,* respectively.

Calculate the quantity, in mg, of phosphate, expressed as monobasic sodium phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), in the volume of Solution taken by the formula:

$$0.001(137.99/94.97)C_S D(r_U / r_S),$$

in which 137.99 is the molecular weight of monobasic sodium phosphate monohydrate; 94.97 is the molecular weight of phosphate (PO_4); C_S is the concentration, in µg per mL, of phosphate in *Standard Preparation 2; D* is the dilution factor; and r_U and r_S are the phosphate peak areas obtained from the *Assay preparation for total phosphate assay* and *Standard Preparation 2,* respectively.■1S (*USP29*)

(Official April 1, 2009)

BRIEFING

Anticoagulant Sodium Citrate Solution, *USP 28* page 168; **Anticoagulant Citrate Dextrose Solution,** *USP 28* page 165 and page 1583 of *PF* 30(5) [Sep.–Oct. 2004]; **Anticoagulant Citrate Phosphate Dextrose Solution,** *USP 28* page 165; **Anticoagulant Citrate Phosphate Dextrose Adenine Solution,** *USP 28* page 166; **Multiple Electrolytes Injection Type 2,** *USP 28* page 717 and page 3220 of the *First Supplement;* **Multiple Electrolytes and Dextrose Injection Type 2,** *USP 28* page 720 and page 3221 of the *First Supplement;* and **Sodium Citrate and Citric Acid Oral Solution,** *USP 28* page 1783. It is proposed to replace all of the assay procedures for citric acid or inorganic citrate and phosphate provided in the respective monographs with a single ion chromatography procedure as described in the proposed general chapter *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩, which was published in *PF* 31(2) [Mar.–Apr. 2005]. In the absence of any significant adverse comment, the revisions are scheduled to appear in the *First Supplement* to *USP 29–NF 24*, but with a delayed implementation date of April 1, 2009.

(BBP: R. Tirumalai; D. Bempong) RTS—42196-1

Change to read:

USP Reference standards ⟨11⟩—

■*USP Citric Acid RS.*■1S (*USP29*)
USP Endotoxin RS.

(Official April 1, 2009)

Change to read:

Assay— ~~Transfer 10.0 mL of Solution to a 250-mL beaker, and evaporate to dryness. Add 100 mL of glacial acetic acid, stir until completely dissolved, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically using a calomel-glass electrode system. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 9.803 mg of $C_6H_8Na_2O_7 \cdot 2H_2O$.~~

In-Process Revision

■*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed for *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Pipet 10 mL of Solution into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under general chapter ⟨345⟩.

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, and calculate the quantity, in mg, of sodium citrate dihydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) in the volume of Solution taken by the formula:

$$0.001(294.10/189.10)C_S D(r_U / r_S),$$

in which 294.10 is the molecular weight of sodium citrate dihydrate; 189.10 is the molecular weight of citrate ($C_6H_5O_7$); C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1, D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.■1S (*USP29*)

(Official April 1, 2009)

BRIEFING

Aprotinin; Aprotinin Injection. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Limit of N-pyroglutamyl-aprotinin and related compounds* are based on analyses performed with the TSK Gel SP-5 PW brand of L52 column. The liquid chromatographic procedures in the test for *Limit of high molecular weight proteins* are based on analyses performed with the Waters Protein-Pak 125 brand of L33 column.

(BNT: L. Callahan) RTS—41730-1; 42056-1; 42090-1

Add the following:

■Aprotinin

$C_{284}H_{432}N_{84}O_{79}S_7$ 6511.44

Aprotinin [*9087-70-1*].

» Aprotinin is a polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein, plasmin, and trypsin. Aprotinin is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilized powder. Its potency calculated on a dried basis is not less than 3 USP Aprotinin Units per mg. In addition, the method of manufacture is validated to result in not more than 0.2 µg of histamine per 3 USP units of aprotinin by validated methods. The origin and sourcing of bovine material must be in compliance with FDA regulations and must fulfill the regulatory requirements for the health of animals for human consumptiion. The manufacturing process is validated to demonstrate the clearance of potential infectious agents (i.e., viruses, TSE agents). One USP Aprotinin Unit is equivalent to 1800 Kallikrein Inhibition Units (K.I.U.).

In-Process Revision

Packaging and storage—For lyophillized powder, preserve in tight containers, and store in a cold place. Protect from light. For bulk solution, preserve in tight containers at a temperature not exceeding 25°. Avoid freezing.

Labeling—The labeling states the source of material and the number of Kallikrein Inhibition Units per mg or the number of Kallikrein Inhibition Units per mL.

USP Reference standards ⟨11⟩**—***USP Aprotinin RS. USP Aprotinin System Suitability RS. USP Endotoxin RS. USP Trypsin Crystallized RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Prepare a solution of Aprotinin in water having a concentration of about 15 USP Aprotinin units per mL.

Developing solvent system: a mixture of glacial acetic acid and water (100 : 80) containing 100 g per L of sodium acetate.

Cupric chloride solution—Dissolve 1 g of cupric chloride in 100 mL of water.

Spray reagent—Dissolve 0.1 g of ninhydrin in a mixture containing 6 mL of *Cupric chloride solution,* 21 mL glacial acetic acid, and 70 mL of alcohol.

Procedure—Proceed as directed in the chapter, except to spray the plate with the *Spray reagent,* and heat at 60° to visualize the spots.

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 *Limit of N-pyroglutamyl-aprotinin and related compounds*.

Absorbance ⟨851⟩**—**Prepare a solution containing 3.0 USP Aprotinin Units per mL. The solution shows an absorption maximum at 277 nm. The absorbance at the maximum is not greater than 0.80.

Safety—Prepare a solution of aprotinin that contains 4 USP units per mL using a sufficient quantity of water for injection. It meets the requirements when tested as directed in the section *Safety Tests—Biologicals* under *Biological Reactivity Tests, In Vivo* ⟨88⟩.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.14 USP Endotoxin Unit per USP Aprotinin Unit. Use solution that contains 6 USP Aprotinin Units per mL.

Loss on drying ⟨731⟩—[NOTE—This test should only be performed on the lyophilized powder.] Dry about 100 mg, accurately weighed, in a capillary-stoppered bottle 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.

Specific activity of the dry residue—[NOTE—This test should only be performed when product is a concentrated solution.] Evaporate 25.0 mL of Aprotinin concentrated solution to dryness in a water bath, dry the residue at 110° for 15 hours, and weigh. From the weight of the residue and the activity determined in the *Assay,* calculate the number of USP Aprotinin Units per mg of dry residue. Not less than 3.0 USP Aprotinin units per mg dried residue is found.

Limit of des-Ala-aprotinin and des-Ala-des-Gly-aprotinin—

Test solution—Dilute a concentrated solution of Aprotinin with water or weigh out Aprotinin, and dissolve in water to obtain a solution containing about 4 to 7 USP Aprotinin Units per ml.

Standard solution—Dilute USP Aprotinin RS with water to obtain a solution having a concentration similar to that of the *Test solution*.

Capillary zone electrophoresis buffer—Dissolve 8.21g of potassium phosphate, monobasic in 400 mL water, adjust with phosphoric acid to a pH of 3.0, and dilute with water to 500 mL.

Capillary zone electrophoresis system (see *Capillary Electrophoresis in Biotechnology-Derived Articles* ⟨1047⟩)—The capillary electropherograph is equipped with a 214-nm detector and a 45 to 60 cm uncoated fused silica capillary with an internal diameter of 75 µm with the temperature controlled at 25°. Apply a field strength of 0.2 kV/cm for 30 minutes, using *Capillary zone electrophoresis buffer* as the electrolyte in both buffer reservoirs. Electropherograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative migration times are about 0.98 for des-Ala-des-Gly-aprotinin, 0.99 for des-Ala-aprotinin, and 1 for aprotinin. The resolution, R_S, between the des-Ala-des-Gly-aprotinin and des-Ala-aprotinin peaks is not less than 0.8, and the resolution between the des-Ala-aprotinin and aprotinin peaks is not less than 0.5. The migration time for the aprotinin peak is between 19 and 25 minutes. The tailing factor, *T,* of the aprotinin peak is not more than 3 (see *Chromatography* ⟨621⟩ for calculation). The baseline is stable and shows little drift. Rinse the capillary for at least 1 minute with at least 10 total capillary volumes of 0.1 N sodium hydroxide, followed by at least 10 total capillary volumes of water, and by at least 20 capillary volumes of *Capillary zone electrophoresis buffer* between injections.

Procedure—Transfer a volume of the *Test solution,* approximately 15 nL, into the anodic end of the capillary (apply differential pressure of 3.5 kPa for 3 seconds either by vacuum or pressure), record an electropherogram, and measure the peak areas. Calculate the percentage contents of des-Ala-des-Gly-aprotinin and des-Ala-aprotinin by the formula:

$$100(r_i / r_S)$$

in which r_i is the peak response corresponding to des-Ala-des-Gly-aprotinin or des-Ala-aprotinin; and r_S is the sum of the responses of des-Ala-des-Gly-aprotinin, des-Ala-aprotinin and aprotinin peaks: not more than 8.0% des-Ala-des-Gly-aprotinin and not more than 7.5% des-Ala-aprotinin is found.

Limit of N-pyroglutamyl-aprotinin and related compounds—

Solution A—Prepare a filtered and degassed solution containing 3.52 g of potassium phosphate, monobasic and 7.26 g of sodium phosphate, dibasic dissolved in 1000 mL of water.

Solution B—Prepare a filtered and degassed solution containing 3.52 g of potassium phosphate, monobasic, 7.26 g of sodium phosphate, dibasic, and 66.07 g of ammonium sulfate dissolved in 1000 mL of water.

Resolution solution—Prepare a solution of USP Aprotinin System Suitability RS containing about 5 USP Aprotinin Units per mL in *Solution A.*

Test solution—Prepare a solution of aprotinin having a concentration of about 5 USP Aprotinin Units per mL. Dilute with *Solution A.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 7.5-mm × 7.5-cm column that contains packing L52 and is maintained at a constant temperature of 40°. The flow rate is 1 mL per minute. The chromatograph is programmed as follows.

In-Process Revision

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–21	92→64	8→36	linear gradient
21–30	64→0	36→100	linear gradient
30–31	0→92	100→8	linear gradient
31–40	92	8	re-equilibration

Chromatograph the *Resolution solution* as directed for *Procedure:* the retention time for aprotinin is between 17 and 20 minutes; the relative retention times are about 0.9 for N-pyroglutamyl-aprotinin, and 1.0 for aprotinin; the resolution, *R,* between N-pyroglutamyl-aprotinin and aprotinin is not less than 1.0; and the tailing factor for the aprotinin peak is not greater than 2.0.

Procedure—Inject 40 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas. Calculate the percentage of each impurity peak in the chromatogram by the formula:

$$100(r_i / r_S)$$

in which r_i is the response of each impurity peak; and r_S is the sum of the responses of all peaks in the chromatogram of the *Test solution:* not more than 1.0% *N*-pyroglutamyl-aprotinin is found; not more than 0.5% of any other impurity is found; and the sum of all unknown impurities is not more than 1.0%.

Limit of high molecular weight proteins—

Mobile phase—Prepare a filtered and degassed mixture of water, glacial acetic acid, and acetonitrile (6 : 2 : 2).

Resolution solution—Prepare an aprotinin solution that contains about 5 USP Aprotinin units per mL with about 2% aprotinin oligomers. [NOTE—This solution can be obtained by heating lyophilized aprotinin at 112° for about 2 hours and dissolving the solid at the specified concentration in water.]

Test solution—Prepare a solution of aprotinin in water that contains about 5 USP units per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a series of three 7.8-mm × 30-cm columns containing packing L33. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution* as directed for *Procedure:* The retention time for aprotinin is between 24.5 and 25.5 minutes; the relative retention times are about 0.9 for the dimer and 1.0 for aprotinin; the resolution, *R,* between the dimer peak and the aprotinin peak is not less than 1.3; and the tailing factor for the aprotinin peak is not greater than 2.5.

Procedure—Inject about 100 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas. Calculate the percentage of each oligomer peak in the chromatogram by the formula:

$$100 r_i / r_S$$

in which r_i is the response of each peak having a retention time less than that of aprotinin monomer; and r_S is the sum of the responses of all peaks: the sum of all oligomers is not more than 1.0%.

Assay—

0.0015 M Borate buffer—Transfer about 0.93 g of boric acid into a 1000-mL volumetric flask, dissolve in 900 mL of water, adjust with 5 N sodium hydroxide to a pH of 8.0, adjust with water to volume, and mix. Transfer 100 mL of this solution into a 1000 mL volumetric flask, adjust with water to volume, and mix.

Assay preparation—Prepare a solution of aprotinin with *0.0015 M Borate buffer* to obtain a solution having about 1.67 USP units per mL (about 0.6 mg per mL).

Trypsin solution—Prepare a solution of USP Crystallized Trypsin RS containing about 4300 USP units per mL, using 0.001 N hydrochloric acid as the solvent. Use a freshly prepared solution, and keep in iced water.

Trypsin and aprotinin solution—To 4.0 mL of the *Trypsin solution,* add 1.0 mL of the *Assay preparation.* Dilute immediately with *0.0015 M Borate buffer* to 40.0 mL. Allow to stand at room temperature for 10 minutes, and then keep in iced water. Use within 6 hours of preparation.

Dilute trypsin solution—Dilute 0.5 mL of the *Trypsin solution* with *0.0015 M Borate buffer* to 10.0 mL. Allow to stand at room temperature for 10 minutes, and then keep in iced water.

Substrate solution—Dissolve 69 mg of N-benzoyl-L-arginine ethyl ester hydrochloride in 10 mL of water. [NOTE—Use within 2 hours.]

Procedure—Mix 9.0 mL of *0.0015 M Borate buffer* and 1.0 mL of *Substrate solution* in a jacketed glass vessel with a capacity of about 30 mL and that contains a stirring device. The lid of the reaction vessel should contain five holes to accommodate the electrodes, the tip of a buret, a tube for the admission of nitrogen, and the introduction of reactants. An automated or manual titration apparatus may be used. Adjust to a pH of 8.0 by the addition of 0.1 N sodium hydroxide VS. Maintain an atmosphere of nitrogen within the vessel, and stir continuously. When the temperature has reached equilibrium at 25 ± 0.1°, add 1.0 mL of *Trypsin and aprotinin solution,* and start a timer. Maintain at a pH of 8.0 by the addition of 0.1 N sodium hydroxide VS, and note the volume added every 30 seconds. Continue the reaction for 6 minutes. Determine the volume of 0.1 N sodium hydroxide added per second, in mL (n_1). Carry out a similar titration using 1.0 mL of the *Dilute trypsin solution*. Determine the volume of 0.1 N sodium hydroxide added per second, in mL (n_2). For the lyophilized powder, calculate the aprotinin activity in USP Aprotinin units per mg using the formula:

$$4000(2n_2 - n_1)/m$$

in which m is the mg of aprotinin used to prepare 1 mL of the *Assay preparation*. For the concentrated solution, calculate the USP Aprotinin Units per mL using the following formula:

$$4000(2n_2 - n_1)D$$

in which D is the dilution factor of the concentrated solution used to prepare the *Assay preparation.* ■1S (*USP29*)

BRIEFING

Aprotinin Injection—See briefing under *Aprotinin.*

(BNT: L. Callahan) RTS—41752-1

In-Process Revision

Add the following:

■Aprotinin Injection

» Aprotinin Injection is a sterile solution of Aprotinin in Water for Injection that also contains sodium chloride. One USP Aprotinin Unit is equivalent to 1800 Kallikrein Inhibition Units

(K.I.U.). It contains not less than 90.0 percent and not more than 110.0 percent of the potency stated on the label, expressed in Kallikrein Inhibition Units per mL.

Packaging and storage—Preserve in single-dose containers, store up to 25°, and avoid freezing.

USP Reference standards ⟨11⟩—*USP Aprotinin RS. USP Aprotinin System Suitability RS. USP Endotoxin RS. USP Trypsin Crystallized RS.*

Identification—

A: 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 *Limit of N-pyroglutamyl-aprotinin and related compounds* under *Aprotinin*.

B: The determination of activity by the *Assay* is based on the specific inhibition of trypsin.

Bacterial endotoxins ⟨85⟩—It contains not more than 0.14 USP Endotoxin Units per USP Aprotinin Unit.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩**:** between 4.5 and 6.5.

Particulate matter ⟨788⟩**:** meets the requirements.

Sodium chloride content—Pipet 5.0 mL of Aprotinin injection into 50 mL of water in a beaker. Add 10 mL of 25% nitric acid. Titrate with 0.1 N silver nitrate VS to a potentiometric endpoint, using a silver combination electrode. Perform a blank determination (see *Titrimetry* ⟨541⟩), and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride: between 42.5 mg and 47.5 mg of sodium chloride is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩ and for *Limit of N-pyroglutamyl-aprotinin and related compounds* under *Aprotinin*.

Limit of high molecular weight proteins—Proceed as directed in the test for *Limit of high molecular weight proteins* under *Aprotinin*. The sum of all oligomers is not more than 1.5%.

Assay—Proceed as directed in the *Assay* under *Aprotinin.* ■1S (*USP29*)

BRIEFING

Aztreonam for Injection, *USP 28* page 211. It is proposed to make changes in the *Procedure* of the *Assay* section for clarification.

(PA7a: B. Gilbert) RTS—42376-1

Change to read:

Assay—

Mobile phase—Dissolve 1.15 g of monobasic ammonium phosphate in about 800 mL of water. Adjust with phosphoric acid to a pH of 2.0 ± 0.1, dilute with water to 1000 mL, and mix. Prepare a suitable mixture of acetonitrile and this solution (750 : 250). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Aztreonam RS and USP L-Arginine RS quantitatively in *Mobile phase* to obtain a solution containing known concentrations of about 0.2 mg of each per mL.

Resolution solution—Prepare a solution in *Mobile phase* containing in each mL about 0.2 mg each of USP Aztreonam RS and USP Open Ring Aztreonam RS.

Assay preparation 1—Weigh accurately 1 container of Aztreonam for Injection. Transfer the contents of the container to a 100-mL volumetric flask. Weigh the empty container, and calculate the weight, in mg, of Aztreonam for Injection removed. Dissolve the powder in the volumetric flask in *Mobile phase*, dilute with *Mobile phase* to volume, and mix. Dilute an accurately measured volume of this solution quantitatively with *Mobile phase* to obtain a solution having a concentration of about 0.2 mg of aztreonam per mL.

Assay preparation 2—Constitute 1 container of Aztreonam for Injection with a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling, except where the capacity of the container is 100 mL or greater to constitute with 10 mL of water. Withdraw the total withdrawable contents of the container, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 0.2 mg of aztreonam per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 206-nm detector, a 4.6-mm × 50-cm saturator precolumn containing packing L27, and a 4-mm × 25-cm analytical column containing packing L20.

The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.8 for aztreonam and 1.0 for open ring aztreonam; the resolution, *R,* between aztreonam and open ring aztreonam is not less than 2.0; the column efficiency as determined from the aztreonam peak is not less than 1000 theoretical plates; the tailing factor for the aztreonam peak 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,*~~

■*Assay preparation 1,* and *Assay preparation 2*■1S (*USP29*) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.3 for aztreonam and 1.0 for arginine. Calculate the percentage of aztreonam ($C_{13}H_{17}N_5O_8S_2$) in the Aztreonam for Injection taken by the formula:

$$0.1(C_S P_S / C_U)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Aztreonam RS in the *Standard preparation;* P_S is the assigned purity, in µg per mg, of the USP Aztreonam RS; C_U is the concentration, in mg per mL, of Aztreonam for Injection in *Assay preparation 1,* based on the weight, in mg, of Aztreonam for Injection removed from the container and the extent of dilution; and r_U and r_S are the aztreonam peak responses obtained from *Assay preparation 1* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of aztreonam ($C_{13}H_{17}N_5O_8S_2$) in the container of Aztreonam for Injection used to prepare *Assay preparation 2* taken by the formula:

$$(C_S P_S L / 1000 C_U)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Aztreonam RS in the *Standard preparation;* P_S is the assigned purity, in µg per mg, of USP Aztreonam RS; L is the labeled quantity, in mg, of aztreonam in the container of Aztreonam for Injection; C_U is the concentration, in mg per mL, of aztreonam in *Assay preparation 2,* on the basis of the labeled quantity, in mg, of aztreonam in the container and the extent of dilution; and r_U and r_S are the aztreonam peak responses obtained from ~~*Assay preparation 1*~~

■*Assay preparation 2*■1S (*USP29*) and the *Standard preparation*, respectively.

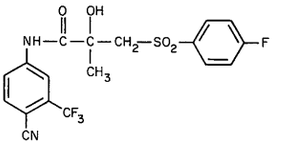
BRIEFING

Bicalutamide. Because there is no existing *USP* monograph for this drug substance, a new monograph based on validated methods is being proposed. The reverse phase HPLC procedures in the test for *Chromatographic purity* are based on analyses performed with a Hypersil ODS brand of L1 column. The typical retention time for bicalutamide is about 17 minutes. The reverse phase HPLC procedures in the *Assay* are based on analyses performed with a Hypersil ODS brand of L1 column. The typical retention time for bicalutamide is about 3 minutes.

(PA6: L. Evans; PSD: C. Okeke; NL: L. Paul) RTS—42222-1; 42222-2; 42222-3

Add the following:

■Bicalutamide



$C_{18}H_{14}F_4N_2O_4S$ 430.37

Propanamide, *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-.

(±)-4′-Cyano-α,α,α-trifluoro-3-[(*p*-fluorophenyl)sulfonyl]-2-methyl-*m*-lactotoluidide [*90357-06-5*].

» Bicalutamide contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{14}F_4N_2O_4S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩—*USP Bicalutamide RS. USP Bicalutamide Related Compound A 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.*

In-Process Revision

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%.

Limit of alcohol—

Standard solution—Prepare a solution of alcohol in dimethyl sulfoxide having a known concentration of about 0.1 mg of alcohol per mL.

Test solution—Dissolve an accurately weighed portion of Bicalutamide in dimethyl sulfoxide to obtain a solution having a concentration of about 100 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.53-mm × 30-m capillary column, the internal wall of which is coated with a 1.0-µm film of liquid phase G43. The carrier gas is helium, flowing at a rate of about 4.4 mL per minute with a split ratio of 1 : 5. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 70° for 2 minutes, then increased at a rate of 20° per minute to 170°, and maintained at 170° for 1 minute. The injector port temperature is maintained at 140°; the headspace sampler temperature is maintained at 80°; and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time for alcohol is about 1.6 minutes; the column effiiciency is not less than 10,000 theoretical plates; and the relative standard deviation for three injections of the *Standard solution* is not more than 5.0%.

Procedure—Transfer 1.0 mL each of the *Test solution* and the *Standard solution* to separate 20-mL headspace vials. Record the chromatograms, and measure the peak area for the alcohol peak. Calculate the amount of alcohol in ppm in the portion of Bicalutamide taken by the formula:

$$10^6(C_S / C_U)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of alcohol in the *Standard solution;* C_U is the concentration, in mg per mL, of Bicalutamide in the *Test solution;* and r_U and r_S are the alcohol peak areas in the chromatograms obtained from the *Test solution* and the *Standard solution,* respectively: not more than 500 ppm of alcohol (C_2H_5OH) is found.

Chromatographic purity—

Solution A, Solution B, and *Diluent*—Prepare as directed in the *Assay.*

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 Bicalutamide Related Compound A RS and USP Bicalutamide RS in *Diluent* to obtain a solution having known concentrations of about 0.005 mg per mL and 0.05 mg per mL, respectively.

Standard solution—Dissolve an accurately weighed quantity of USP Bicalutamide RS in *Diluent* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Transfer about 25 mg of Bicalutamide, 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 270-nm detector and a 4.0-mm × 10-cm column that contains 3-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
0–16.5	67	33	isocratic
16.5–26.5	67→40	33→60	linear gradient
26.5–32.5	40→5	60→95	linear gradient
32.5–32.6	5→67	95→33	linear gradient
32.6–35.0	67	33	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.62 for bicalutamide related compound A isomer A, 0.65 for bicalutamide related compound A isomer B, and 1.0 for bicalutamide; and the resolution, *R,* between bicalutamide related compound A isomer A and bicalutamide related compound A isomer B is not less than 0.8, and the resolution, *R,* between bicalutamide related compound A isomer B and bicalutamide is not less than 8.5.

Procedure—Separately inject equal volumes (about 10 µL) of the *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 Bicalutamide taken by the formula:

$$2.5(CW)(r_i / r_S),$$

in which C is the concentration, in µg per mL, of USP Bicalutamide RS in the *Standard solution; W* is the weight, in mg, of Bicalutamide in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the bicalutamide peak response obtained from the *Standard solution*. Disregard any peak less than 0.02%: not more than 0.10% of any individual impurity is found; and not more than 0.50% of total impurities is found.

Assay—

Solution A—Prepare a filtered and degassed 0.01% (v/v) solution of trifluoroacetic acid in water.

Solution B—Prepare a filtered and degassed 0.01% (v/v) solution of trifluoroacetic acid in acetontrile.

Diluent—Prepare a mixture of *Solution A* and *Solution B* (1 : 2).

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *Solution B* (52 : 48). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Bicalutamide RS and USP Bicalutamide Related Compound A RS in *Diluent* to obtain a solution having known concentrations of about 0.05 mg per mL and 0.005 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Bicalutamide RS in *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Transfer about 25 mg of Bicalutamide, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix. Pipet 1.0 mL of this solution into a 20-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 270-nm detector and a 4.0-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between bicalutamide related compound A isomer B and bicalutamide is not less than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

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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 $C_{18}H_{14}F_4N_2O_4S$ in the portion of Bicalutamide taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Bicalutamide 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 (*USP29*)

BRIEFING

Bismuth Subsalicylate Tablets, page 1167 of *PF* 30(4) [July–Aug. 2004]. It is proposed to add a test for *Disintegration* to this proposed new monograph.

(BPC: M. Marques) RTS—42316-1

Add the following:

■Bismuth Subsalicylate Tablets

» Bismuth Subsalicylate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of bismuth subsalicylate ($C_7H_5BiO_4$).

Packaging and storage—Preserve in tight containers. Store between 15° and 30°.

Labeling—Label chewable Tablets to indicate that they are to be chewed before swallowing.

Identification—

A: It meets the requirements of the tests for *Bismuth* ⟨191⟩.

B: After acidifying with nitric acid, it meets the requirements of the test for *Salicylate* ⟨191⟩ with ferric chloride TS.

Disintegration ⟨701⟩**:** 10 minutes. [NOTE—This test does not apply for Tablets labeled as chewable.]

Assay—

Standard preparation—Transfer about 500 mg of bismuth, accurately weighed, to a 200-mL volumetric flask, dissolve in 12 mL of nitric acid, and dilute with 0.01 N nitric acid to volume. Transfer 10.0 mL of the solution so obtained into a 500-mL volumetric flask, and dilute with 1 N nitric acid to volume to obtain a concentration of 50 µg of bismuth per mL.

Assay preparation—Transfer an accurately weighed portion of finely powdered Tablets, equivalent to about 90 mg of bismuth subsalicylate, to a 200-mL volumetric flask, add about 150 mL of 1 N nitric acid, and sonicate for 2 minutes. Dilute with 1 N nitric acid to volume. Transfer 20.0 mL of the solution so obtained to a 100-mL volumetric flask, and dilute with 1 N nitric acid to volume. Centrifuge a portion at 4500 rpm for at least 10 minutes.

Procedure—Transfer 10.0 mL, accurately measured, of the *Assay preparation* and the *Standard preparation* to separate 50.0-mL volumetric flasks. Add 10.0 mL of 10% ascorbic acid solution and 25.0 mL of 20% potassium iodide solution into each volumetric flask, and dilute with 1 N nitric acid to volume. Concomitantly determine the absorbance of the solutions at the wavelength of maximum absorbance at about 463 nm with a suitable spectrophotom-

eter using the combined reagent solutions as the blank. Calculate the quantity, in mg, of $C_7H_5BiO_4$ in the portion of Tablets taken by the formula:

$$(362.11/208.98)(C)(A_U/A_S),$$

in which 362.11 and 208.98 are the molecular weights of bismuth subsalicylate and bismuth, respectively; C is the concentration, in ~~µg~~ mg per mL, of bismuth 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.■1S (*USP29*)

BRIEFING

Buspirone Hydrochloride, *USP 28* page 299. It is proposed to revise the test for *Content of chloride* to clarify that the content is measured using residual titration (also known as back titration).

(PA3: R. Ravichandran) RTS—42392-1

Change to read:

Content of chloride—Dissolve about 400 mg, accurately weighed, in 20 mL of water. Add 3 mL of nitric acid and 20.0 mL of 0.1 N silver nitrate VS. Gently boil the mixture for about 5 minutes. Filter, rinse the flask with about 80 mL of water divided into small portions, and filter each portion. Add 2 mL of 8% ferric ammonium sulfate. ~~and stir rapidly while titrating from a buret with 0.1 N ammonium thiocyanate VS to a faint red-brown endpoint.~~

■While stirring rapidly, titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS from a buret to a faint red-brown endpoint. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩.■1S (*USP29*)
Each mL of 0.1 N silver nitrate

■consumed■1S (*USP29*)
is equivalent to 3.545 mg of chloride: between 8.0% and 8.8% is found.

BRIEFING

Camphor, *USP 28* page 334. It is proposed to change the name of the test from *Water* to *Appearance of solution* to accurately reflect this procedure.

(PA7b: B. Davani) RTS—42258-1

Change to read:

~~**Water—**~~

■**Appearance of solution**—■1S (*USP29*)
A 1 in 10 solution in solvent hexane is clear.

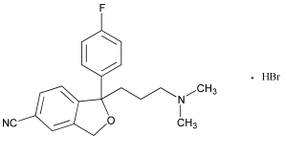
BRIEFING

Citalopram Hydrobromide. Because there is no existing *USP* monograph for this drug substance, a new monograph is proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the YMC Basic column. Typical retention times are about 28 minutes for citalopram and 25 minutes for citalopram related compound D.

(PA3: R. Ravichandran; NL: L. Paul; PSD: C. Okeke) RTS—41833-1; 41833-3; 41833-4

Add the following:

■Citalopram Hydrobromide



$C_{20}H_{21}FN_2O \cdot HBr$ 405.30

5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, monohydrobromide.

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1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile monohydrobromide [*59729-32-7*].

» Citalopram Hydrobromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{21}FN_2O \cdot HBr$, calculated on an anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Citalopram Hydrobromide RS. USP Citalopram Hydrobromide Related Compound D RS.*

Completeness of solution—The absorbance at 410 nm of a 2.5% w/v solution, in 96% alcohol, against a sample solvent in a 1-cm quartz cell is not more than 0.040.

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: A solution of 10 mg per mL meets the requirements of the test for *Bromide* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –0.2° and +0.2° at 20°.

Test solution: 25 mg per mL, in methanol.

pH ⟨791⟩**:** between 5.5 and 6.5, in a solution (0.5 in 100).

Water, *Method I* ⟨921⟩**:** not more than 0.5% using about 250 mg of sample.

Residue on ignition ⟨281⟩**:** not more than 0.1%. The sample is moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Buffer, Mobile phase, Diluent, and *Chromatographic system*—Prepare as directed in the *Assay.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Use the *Standard preparation,* as prepared in the *Assay.*

Working standard solution—Prepare a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard solution* with *Mobile phase.*

System suitability solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.001 mg per mL.

Sensitivity solution—Dilute 5.0 mL of the *Working standard solution* with *Diluent* to 50 mL to obtain a solution having 0.0625 µg of citalopram hydrobromide per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Inject the *Diluent* as directed for *Procedure* to verify that there are no interfering peaks. Inject the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is at least 3. Inject the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 0.90 for citalopram related compound D and 1.0 for citalopram hydrobromide; the resolution, *R,* between citalopram related compound D and citalopram is not less than 1.8; the column efficiency is not less than 7000 theoretical plates for citalopram; the tailing factor for the citalopram hydrobromide peak is not less

than 0.8 and not more than 1.5; and the relative standard deviation for replicate injections is not more than 5% based on the citalopram peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms for about 40 minutes, and measure the responses for the major peaks. Calculate the percentage of related compounds in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_T)(r_i / r_S)(324.39/405.30)(1/F),$$

in which C_S and C_T are the concentrations, in mg per mL, of Citalopram Hydrobromide in the *Working standard solution* and the *Test solution,* respectively; r_i is the peak response for each impurity obtained from the *Test solution;* r_S is the peak response for the citalopram peak, obtained from the *Working standard solution;* 324.39 and 405.30 are the molecular weights for citalopram and citalopram hydrobromide; and F is the relative response factor for each impurity relative to citalopram (free base) as presented in *Table 1.*

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
1-(3-Dimethylaminopropyl)-1-(4′-fluorophenyl)-5-(4-dimethylaminobutyryl)-1,3-dihydrobenzofuran	0.13	0.34	NMT* 0.1
Citalopram related compound A	0.18	0.77	NMT 0.1
4-[4-Dimethylamino-1-(4′-fluorophenyl)-1-hydroxy-1-butyl]-3-hydroxymethyl benzonitrile	0.26	0.99	NMT 0.1
Citalopram related compound B	0.40	0.98	NMT 0.1
Citalopram related compound C	0.67	0.69	NMT 0.1
Citalopram related compound D	0.90	1.04	NMT 0.1
Citalopram hydrobromide	1.0	1.0	—
Citalopram related compound E	1.29	0.91	NMT 0.1
Unkown	—	1.0	NMT 0.1 each
Total known and unknown	—	—	NMT 0.2

* NMT = not more than.

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Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Assay—

Buffer—In a 1-L volumetric flask, dissolve about 1 g of sodium acetate in 800 mL of water, and add 6 mL of triethylamine. Adjust with acetic acid to a pH of 4.6, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (80 : 20). The apparent pH is 5.0 ± 0.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (1 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.625 mg per mL.

Assay preparation—Transfer about 62.5 mg of Citalopram Hydrobromide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix to obtain a solution containing 0.625 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 150-mm × 4.6-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 50°. Inject the *Diluent* to verify that there are no interfering peaks. Inject the *Standard preparation,* and record the peak responses as directed for *Procedure*: the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 3.0; 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 for about 30 minutes, and measure the responses for the major peaks. Calculate the quantity, in percent of $C_{20}H_{21}FN_2O \cdot HBr$ in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_U)(r_U / r_S),$$

in which C_S and C_U are the concentrations, in mg per mL, of the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

BRIEFING

Citalopram Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is proposed. The proposed liquid chromatographic procedures in the *Assay* are performed with the Spherisorb ODS 1 column; the test for *Related compounds* uses an Inertsil-2 ODS column. The typical retention time for citalopram is about 6 minutes.

(PA3: R. Ravichandran; NL: L. Paul; PSD: Claudia Okeke) RTS—41833-2; 41833-5; 41833-6

Add the following:

■Citalopram Tablets

» Citalopram Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of citalopram free base ($C_{20}H_{21}FN_2O$).

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Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Citalopram Hydrobromide RS. USP Citalopram Related Compound A RS. USP Citalopram Related Compound B RS. USP Citalopram Related Compound C RS. USP Citalopram Related Compound E RS. USP Citalopram Related Compound F RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Extract finely ground Tablet powder containing about 200 mg of citalopram with 30 mL of water, and filter. Add 1 mL of 1 N sodium hydroxide, and extract with 50 mL of cyclohexane by shaking for 10 minutes. Pass the cyclohexane layer through a silicone treated filter paper into a beaker. Reduce the filtrate down to 3 mL using gentle heat as necessary. Transfer the hot solution to a small centrifuge tube. Induce crystallization while cooling by scratching the side of the test tube with a spatula. Centrifuge the mixture, and decant off the cyclohexane. Dry the residue under vacuum in a desiccator. Mix approximately 2 mg of the residue with approximately 300 mg of potassium bromide, and record the IR spectrum.

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: A solution of 2 mg per mL equivalent of citalopram in water meets the requirements of the test for *Bromide* ⟨191⟩.

Dissolution ⟨711⟩—[To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Buffer, Diluent, Internal standard solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add 10 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 40 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature. Add sufficient volume of *Internal standard solution,* and dilute, stepwise if necessary, with *Diluent* to volume to obtain a *Test solution* having a concentration of about 0.1 mg per mL of citalopram and 0.025 mg per mL of internal standard. Pass a portion of this solution through a membrane filter (PVDF) having a 0.45-µm or finer porosity, and use the filtrate.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Procedure—Proceed as directed in the *Assay.* Calculate the quantity, in mg, of $C_{20}H_{21}FN_2O$ in the portion of sample taken by the formula:

$$100(CV)(R_U / R_S)(324.39/405.30),$$

in which C is the concentration, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard solution; V* is the final volume, in mL, required to obtain the *Test solution;* R_U and R_S are the ratio of peak responses of citalopram to the internal standard in the *Test solution* and *Standard solution,* respectively; and 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively.

Related compounds—

Phosphate buffer—Dissolve 3.15 g of potassium dihydrogen phosphate and 3.60 g of disodium hydrogen phosphate ($Na_2HPO_412H_2O$) in 1 L of water.

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Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer,* methanol, and acetonitrile (55 : 38 : 7). Adjust with phosphoric acid to a pH of 6.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard solution—Prepare a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard stock solution* with *Mobile phase*.

Sensitivity solution—Prepare a solution having a concentration of 0.05 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard solution* with *Mobile phase*.

Related compounds stock solutions—Separately dissolve accurately weighed quantities of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Citalopram Related Compound E RS in *Mobile phase* to obtain stock solutions having known concentrations of about 0.1 mg per mL of each compound.

Peak identification solution—Prepare a mixture containing about 0.001 mg per mL of each of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Citalopram Related Compound E RS using the *Standard stock solution* as the diluent.

Resolution solution—Dilute 0.5 mL of *Citalopram related compound C stock solution* and 25.0 mL of the *Standard stock solution* with *Mobile phase* to 50 mL to obtain a solution containing 0.01 mg per mL of citalopram related compound C and 0.25 mg per mL of citalopram hydrobromide.

Test solution—Transfer 10 Tablets into a 200-mL volumetric flask, add 25 mL of *Phosphate buffer,* and shake by mechanical means until disintegrated. Add about 100 mL of a mixture of methanol and water (50 : 50), mix and sonicate for about 5 minutes. Allow to cool, dilute with a mixture of methanol and water (50 : 50) to volume, and mix thoroughly. Allow the excipients to settle. Dilute as necessary to obtain a final concentration of 0.5 mg per mL of citalopram. Pass a portion of this solution through a polytetrafluoroethylene (PTFE) membrane filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with 239-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 45°. The flow rate is about 0.8 mL per minute. Inject the *Standard solution,* and record the peak responses as directed for *Procedure*: the citalopram peak shows no shoulders or excessive tailing; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 1.5; the capacity factor, k', is not less than 3.5; the relative standard deviation of both the retention time and the response for replicate injections is not more than 5%. Inject the *Sensitivity solution* into the chromatographic system and verify that the signal-to-noise ratio is at least 3. Inject the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, R, between citalopram related compound C and citalopram is not less than 3. Inject the *Peak identification solution,* and record the responses as directed for *Procedure:* the four related compound peaks are baseline resolved from each other and the citalopram peak.

Procedure—Inject a volume (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 each Tablet by the formula:

$$100(r_i / r_S)(324.39/405.30)(C_S / C_T)(1/F),$$

in which r_i is the individual peak response for each citalopram related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; F is the relative response factor of each impurity relative to citalopram (free base); and C_S and C_T are the concentrations, in mg per mL, of citalopram hydrobromide in the *Standard solution* and the *Test solution,* respectively. The limits for the related compounds are listed in *Table 1.*

Table 1

Related Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Citalopram related compound A	0.43	0.77	NMT* 0.1
Citalopram related compound B	0.60	0.98	NMT 0.25
Citalopram related compound C	0.83	0.69	NMT 0.25
Citalopram related compound E	1.32	0.91	NMT 0.1
Unknown	—	1.0	NMT 0.1 each
Total known and unknown	—	—	NMT 0.7

* NMT = not more than.

Assay—

Buffer—Transfer about 0.71 g of anhydrous dibasic sodium phosphate to a 500-mL volumetric flask, add about 250 mL of water. Shake to dissolve, then dilute with water to volume.

Diluent—Prepare a solution of methanol and *Buffer* (80 : 20).

Internal standard solution—Dissolve an accurately weighed amount of USP Citalopram Related Compound F RS in *Diluent* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.25 mg per mL.

Mobile phase—Prepare a filtered and degassed solution of *Diluent* containing about 770 mg of dodecyltrimethylammonium bromide per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1.25 mg of citalopram hydrobromide per mL.

Standard preparation—Pipet 5.0 mL of the *Standard stock preparation* and 5.0 mL of the *Internal standard solution* into a 50-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer 10 Tablets to a 200-mL volumetric flask, add 25 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 100 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature, then dilute with *Diluent* to volume. Allow to stand until the residue settles before taking an aliquot for dilution. Transfer an accurately measured volume of the upper clear solution to a 50-mL volumetric flask to obtain a final concentration equivalent to between 0.090 and 0.10 mg per mL

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of citalopram. Add 5.0 mL of *Internal standard solution,* dilute with *Diluent* to volume, and mix. Pass a portion through a filter (PTFE) having a 0.45-µm or finer porosity.

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 column temperature is maintained at 45°. Inject the *Standard preparation,* and record the peak responses as directed for *Procedure*: the relative retention times are about 1.36 for citalopram related compound F and 1.0 for citalopram; the resolution, *R,* between citalopram and citalopram related compound F is not less than 1.5; the column efficiency is not less than 2000 theoretical plates, calculated from the citalopram peak; and the relative standard deviation for replicate injections is not more than 1.5% for the citalopram peak.

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 citalopram peaks. Calculate the quantity, in percent of label claim, of citalopram per Tablet taken by the formula:

$$100(C_S / C_U)(324.39/405.30)(R_U / R_S),$$

in which C_S and C_U are the concentrations, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard preparation* and Citalopram Hydrobromide the *Assay preparation,* respectively; 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; R_U and R_S are the ratio of peak responses of citalopram to the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

BRIEFING

Anhydrous Citric Acid, *USP 28* page 483 and page 607 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to change the reagent used in the test for *Sulfates* from dibasic potassium sulfate to potassium sulfate.

(EMC: J. Lane) RTS—42402-2

Add the following:

■**Packaging and storage—**Preserve in tight containers. No storage requirements specified.■2S (*USP28*)

Change to read:

Sulfate—

Standard sulfate solution A—To 181 mg of ~~dibasic~~

■■1S (*USP29*)
potassium sulfate in a 100-mL volumetric flask, add a few mL of 30% alcohol, swirl to dissolve, dilute with 30% alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with 30% alcohol to volume, and mix. This solution contains 10 µg of sulfate per mL.

Standard sulfate solution B—To 181 mg of ~~dibasic~~

■■1S (*USP29*)
potassium sulfate in a 100-mL volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with water to volume, and mix. This solution contains 10 µg of sulfate per mL.

Citric acid solution—Dissolve 2.0 g of Anhydrous Citric Acid in about 10 mL of water, dilute with water to 30 mL, and mix.

Procedure—To 4.5 mL of *Standard sulfate solution A* add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the *Citric acid solution* and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of *Standard sulfate solution B* instead of the *Citric acid solution:* any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015%).

Delete the following:

●~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.~~●4

In-Process Revision

BRIEFING

Citric Acid Monohydrate, *USP 28* page 485 and page 607 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to change the reagent used in the test for *Sulfates* from dibasic potassium sulfate to potassium sulfate.

(EMC: J. Lane) RTS—42402-1

Add the following:

■**Packaging and storage—**Preserve in tight containers. No specific storage requirements specified.■2S (*USP28*)

Change to read:

Color of solution—

Standard stock solutions—Prepare three solutions, *A, B,* and *C,* containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g per L):

A—2.4 : 0.6 : 0 : 7.0
B—2.4 : 1.0 : 0.4 : 6.2
C—9.6 : 0.2 : 0.2 : 0

•*Standard solutions*—[NOTE—Prepare the *Standard solutions* immediately before use.] Transfer 2.5 mL of *Standard stock solution A* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution A*. Transfer 2.5 mL of *Standard stock solution B* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution B*. Transfer 0.75 mL of *Standard stock solution C* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution C*.•[4]

Test solution—Use the *Test solution* prepared in the *Clarity of solution* test.

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 A, Standard solution B, Standard solution C,* and water to separate matching test tubes. Compare the *Test solution, Standard solution A, Standard solution B, Standard solution C,* and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* is not more intensely colored than *Standard solutions A, B, C* or water.

Change to read:

Sulfate—

Standard sulfate solution A—To 181 mg of ~~dibasic~~ ■potassium sulfate■1S (*USP29*) in a 100-mL volumetric flask, add a few mL of 30% alcohol, swirl to dissolve, dilute with 30% alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with 30% alcohol to volume, and mix. This solution contains 10 µg of sulfate per mL.

Standard sulfate solution B—To 181 mg of ~~dibasic~~ ■potassium sulfate■1S (*USP29*) in a 100-mL volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a 1000-mL volumetric flask, dilute with water to volume, and mix. This solution contains 10 µg of sulfate per mL.

Citric acid solution—Dissolve 2.0 g of Citric Acid Monohydrate in about 10 mL of water, dilute with water to 30 mL, and mix.

Procedure—To 4.5 mL of *Standard sulfate solution A* add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the *Citric acid solution* and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of *Standard sulfate solution B* instead of the *Citric acid solution:* any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015%).

BRIEFING

Dapsone, *USP* 28 page 572. It is proposed to change the composition of the *Mobile phase* in the *Assay* to enhance the precision of the *Procedure.* It is also proposed to use this *Mobile phase* rather than the mixture of methanol and *Mobile phase* in the *Standard preparation* and the *Assay preparation* to eliminate the observed negative peaks.

(PA7b: B. Davani) RTS—42254-1

Change to read:

Assay—

Mobile phase—Transfer 100 mL of isopropyl alcohol, 100 mL of acetonitrile, and 100 mL of ethyl acetate to a 1000-mL volumetric flask. Add ~~pentane~~ ■hexane■1S (*USP29*) to volume without mixing, then mix, and allow the mixture to cool to room temperature.

Standard preparation—Dissolve an accurately weighed quantity of USP Dapsone RS in ~~methanol~~ ■*Mobile phase*■1S (*USP29*)

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to obtain a solution having a known concentration of about 250 µg per mL. Pipet 5 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 25 µg per mL.

Assay preparation—Transfer about 50 mg of Dapsone, accurately weighed, to a 200-mL volumetric flask. Dissolve ~~in methanol, dilute with methanol~~

■in and dilute with *Mobile phase*■1S (*USP29*) to volume, and mix. Pipet 5 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains 10-µm diameter packing L3. Chromatograph a sufficient number of injections of the *Standard preparation* as directed for *Procedure:* the relative standard deviation is not more than 2%.

Procedure—Separately introduce 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, adjusting the specimen size and other operating parameters to obtain satisfactory chromatograms. Measure the responses for the major peaks obtained at corresponding retention times with the *Assay preparation* and the *Standard preparation*. Calculate the quantity, in mg, of $C_{12}H_{12}N_2O_2S$ in the portion of Dapsone taken by the formula:

$$2C(P_U / P_S),$$

in which C is the concentration, in µg per mL, of USP Dapsone RS in the *Standard preparation;* and P_U and P_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Diclofenac Sodium Delayed-Release Tablets, *USP 28* page 626, the *Second Interim Revision Announcement* on page 324 of *PF* 31(2) [Mar.–Apr. 2005], and page 1986 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to add an *Identification* test for *Sodium* to this monograph.

(PA2: C. Anthony) RTS—40020-1

Change to read:

Identification—

■**A:** ■1S (*USP29*)
The retention time of the diclofenac 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 flame test for *Sodium* ⟨191⟩.■1S (*USP29*)

Change to read:

Drug release, *Method B* ⟨724⟩—
ACID STAGE—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2 (paddles constructed of, or coated with, polytef being used): 50 rpm.
Procedure—At the end of 2 hours, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the *Buffer stage*. To the 0.1 N hydrochloric acid remaining in each vessel, add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer ~~2.0 mL~~

■3.0 mL■2S (*USP28*) of this solution to a second 100-mL volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900 : 20) to volume, and mix. This Standard solution contains about 13.6 µg of USP Diclofenac Sodium RS per mL.
BUFFER STAGE—
pH 6.8 Phosphate buffer—Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution. Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.
Medium: pH 6.8 Phosphate buffer; 900 mL.
Apparatus 2: 50 rpm.
Procedure—At the end of 45 minutes, determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with *Medium,* in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a second 100-mL volumetric flask, dilute with *Medium,* as obtained in the *Buffer stage,* to volume, and mix. This Standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL.
Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{14}H_{10}Cl_2NNaO_2$ is dissolved.

Change to read:

•**Dissolution** ⟨711⟩—Proceed as directed for *Procedure* for *Method B* under *Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms.*•2
ACID STAGE—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2 (paddles constructed of, or coated with, polytef being used): 50 rpm.
Procedure—At the end of 2 hours, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the *Buffer stage*. To the 0.1 N hydrochloric acid remaining in each vessel, add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer ~~2.0 mL~~

■3.0 mL■2S *(USP28)* of this solution to a second 100-mL volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide (900 : 20) to volume, and mix. This Standard solution contains about 13.6 µg of USP Diclofenac Sodium RS per mL.

BUFFER STAGE—

pH 6.8 Phosphate buffer—Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution. Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05.

Medium: pH 6.8 Phosphate buffer; 900 mL.

Apparatus 2: 50 rpm.

Procedure—At the end of 45 minutes, determine the amount of $C_{14}H_{10}Cl_2NNaO_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with *Medium*, in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a second 100-mL volumetric flask, dilute with *Medium*, as obtained in the *Buffer stage,* to volume, and mix. This Standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{14}H_{10}Cl_2NNaO_2$ is dissolved.

●(Official April 1, 2006)●2

BRIEFING

Docusate Calcium, *USP 28* page 683—See briefing under *Docusate Sodium.*

(PA4: E. Gonikberg) RTS—42224-4

In-Process Revision

Change to read:

Limit of bis(2-ethylhexyl)maleate—

~~*Electrolyte solution*—In a 250-mL borosilicate glass beaker dissolve 21.2 g of lithium perchlorate in 175 mL of water, and adjust by the dropwise addition of glacial acetic acid to a pH of 3.0. Transfer to a 200-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Sample stock solution*—Transfer the equivalent of 12.5 g of anhydrous Docusate Calcium, accurately weighed, to a 150-mL beaker, add about 85 mL of isopropyl alcohol, stir to dissolve, and transfer to a 250-mL volumetric flask. Rinse the beaker with another 85-mL portion of isopropyl alcohol, stirring, if necessary, to dissolve any residual Docusate Calcium, combine the rinsing with the solution in the volumetric flask, dilute with isopropyl alcohol to volume, and mix.~~

~~*Standard solution*—Transfer 25 mg of USP Bis(2-ethylhexyl) maleate RS, accurately weighed, to a 25-mL volumetric flask, dissolve in isopropyl alcohol, dilute with isopropyl alcohol to volume, and mix. In a second 100-mL volumetric flask combine 10.0 mL of this solution, 50.0 mL of *Sample stock solution*, and 20.0 mL of *Electrolyte solution*, mix, and allow to stand for 2 minutes. Dilute with isopropyl alcohol to volume, and mix.~~

~~*Test solution*—In a 100-mL volumetric flask combine 50.0 mL of *Sample stock solution* with 20.0 mL of *Electrolyte solution*, mix, and allow to stand for 2 minutes. Dilute with isopropyl alcohol to volume, and mix.~~

~~*Procedure*—Transfer a portion of the *Test solution* to a polarographic cell, and deaerate by bubbling through the solution, for 15 minutes, nitrogen that has previously been passed through isopropyl alcohol. Continue to flush the surface of the solution with the nitrogen, insert the dropping mercury electrode of a suitable polarograph (see *Polarography* ⟨801⟩), and record the polarogram from −0.9 to −1.5 volts, using a saturated calomel electrode as the reference electrode. Determine the height of the polarogram at the half-wave potential, at about −1.2 volts, measuring from the baseline. From this height subtract the height, at the same potential, of the polarogram obtained from a blank solution prepared by diluting 20.0 mL of *Electrolyte solution* with isopropyl alcohol to 100 mL in a volumetric flask and mixing. Designate this corrected height as H_u. Concomitantly and similarly determine the height of the polarogram of the *Standard solution,* and subtract the blank value from it. Designate the result as H_s. The value, H_u, is not greater than one-half H_s, corresponding to not more than 0.4% of bis(2-ethylhexyl) maleate.~~

■*Mobile phase, Standard solution,* and *Chromatographic system*—Proceed as directed under *Docusate Sodium*.

Test solution—Transfer about 1.0 g of Docusate Calcium, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with ethanol to volume, and mix. If necessary, warm the mixture using the steam bath to achieve a complete dissolution.

Procedure—Separately inject equal volumes (about 3 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the bis(2-ethylhexyl)maleate peaks. Calculate the percentage of bis(2-ethylhexyl)maleate in the portion of Docusate Calcium taken by the formula:

$$5C/W(r_U / r_S),$$

in which C is the concentration, in µg per mL, of USP Bis(2-ethylhexyl)maleate RS in the *Standard solution; W* is the weight, in mg, of Docusate Calcium taken to prepare the *Test solution;* and r_U and r_S are the peak responses of bis(2-ethylhexyl)maleate obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.4% is found.■1S *(USP29)*

BRIEFING

Docusate Potassium, *USP 28* page 684—See briefing under *Docusate Sodium*.

(PA4: E. Gonikberg) RTS—42224-3

Change to read:

Limit of bis(2-ethylhexyl) maleate—~~Place 12.5 g of Docusate Potassium, previously dried and accurately weighed, in a 100-mL volumetric flask. Pipet 20 mL of pH 10 alkaline borate buffer (see under *Solutions* in the section *Reagents, Indicators, and Solutions*) into the flask, and add about 70 mL of alcohol. Swirl the flask and contents, with gentle warming if necessary, until the solid dissolves. Adjust the reaction dropwise, if necessary, with 1 N sodium hydroxide to a pH of 10. Add alcohol to volume, and proceed as directed in the test for *Bis(2-ethylhexyl)maleate* under *Docusate Sodium,* beginning with "Transfer a portion of this solution to a polarographic cell." The diffusion current for the test solution of Docusate Potassium is not greater than one-half the diffusion current of the solution containing the added bis(2-ethylhexyl)maleate [not more than 0.4% of bis(2-ethylhexyl)maleate].~~

■*Mobile phase, Standard solution,* and *Chromatographic system*—Proceed as directed under *Docusate Sodium.*

Test solution—Transfer about 1.0 g of Docusate Potassium, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with ethanol to volume, and mix. If necessary, warm the mixture using the steam bath to achieve a complete dissolution.

Procedure—Separately inject equal volumes (about 3 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the bis(2-ethylhexyl)maleate peaks. Calculate the percentage of bis(2-ethylhexyl)maleate in the portion of Docusate Potassium taken by the formula:

$$5C/W(r_U / r_S),$$

in which C is the concentration, in µg per mL, of USP Bis(2-ethylhexyl)maleate RS in the *Standard solution; W* is the weight, in mg, of Docusate Potassium taken to prepare the *Test solution;* and r_U and r_S are the peak responses of bis(2-ethylhexyl)maleate obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.4% is found.■1S (*USP29*)

BRIEFING

Docusate Sodium, *USP 28* page 685; **Docusate Calcium,** *USP 28* page 683; **Docusate Potassium,** *USP 28* page 684. It is proposed to replace the current test for *Limit of bis(2-ethylhexyl)maleate* with a simple HPLC procedure that eliminates the use of a polarograph, an instrument which is no longer widely employed because of environmental concerns associated with mercury handling and disposal. The liquid chromatographic procedure is based on analyses performed with a Zorbax XDB-C18 Rapid Resolution brand of L1 column. The typical retention time for bis(2-ethylhexyl)maleate is about 1.5 minutes; docusate elutes at the void volume at about 0.4 minutes.

(PA4: E. Gonikberg) RTS—42224-1; 42224-2

Change to read:

Limit of bis(2-ethylhexyl)maleate—~~Place 12.5 g of Docusate Sodium, previously dried at 105° for 2 hours and accurately weighed, in a 100-mL volumetric flask. Pipet 20 mL of pH 10 alkaline borate buffer (see under *Solutions* in the section *Reagents, Indicators, and Solutions*) into the flask, and add about 70 mL of alcohol. Swirl the flask and contents, with gentle warming, until the solid dissolves. Cool, and add alcohol to volume. Transfer a portion of this test solution to a polarographic cell that is immersed in a water bath regulated at 25 ± 0.5°, and deaerate by bubbling through the solution, for 10 minutes, purified nitrogen that previously has been passed through a solution prepared by mixing 4 volumes of alcohol and 1 volume of water. Insert the dropping mercury electrode of a suitable polarograph, and record the polarogram from −0.5 volt to −1.6 volts, using a saturated calomel electrode as the reference electrode (see *Polarography* ⟨801⟩). Determine the height of the diffusion current at the current plateau at about −1.45 volts. To a separate 50-mL portion of the solution add 25 mg of USP Bis(2-ethylhexyl)maleate RS, accurately weighed, and when solution is complete, deaerate a portion of the resulting solution, and record the polarogram, as directed in the foregoing. The diffusion current for the test solution of Docusate Sodium is not greater than one-half the diffusion current of the solution containing the added USP Bis(2-ethylhexyl)maleate RS [not more than 0.4% of bis(2-ethylhexyl) maleate].~~

■*Mobile phase*—Prepare a filtered and degassed mixture of ethanol and water (78 : 22). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Standard solution—Dissolve an accurately weighed quantity of USP Bis(2-ethylhexyl)maleate RS in ethanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 80 µg per mL.

Test solution—Transfer about 1.0 g of Docusate Sodium, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with ethanol to volume, and mix. If necessary, warm the mixture using the steam bath to achieve a complete dissolution.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 3-cm column that contains 3.5-µm packing L1. The column temperature is maintained at 30°. The flow rate is about 1.0 mL per minute. 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 3 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the bis(2-ethylhexyl)maleate peaks. Calculate the percentage of bis(2-ethylhexyl)maleate in the portion of Docusate Sodium taken by the formula:

$$5C/W(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Bis(2-ethylhexyl)maleate RS in the *Standard solution; W* is the weight, in mg, of Docusate Sodium taken to prepare the *Test solution;* and r_U and r_S are the peak responses of bis(2-ethylhexyl)maleate obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.4% is found. ■1S (*USP29*)

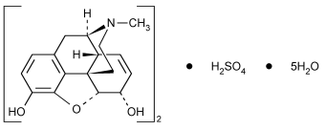
BRIEFING

Drospirenone. 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 *Chromatographic purity* are based on analyses performed with the Symmetry brand of L1 column.

(PA1: C. Anthony) RTS—41672-1

Add the following:

■Drospirenone



$C_{24}H_{30}O_3 \cdot 5H_2O$ 366.49

(6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione. 17-Hydroxy-6*β*,7*β*:15*β*,16*β*-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone [*67392-87-4*].

» Drospirenone contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{30}O_3$, calculated on the anhydrous, solvent-free basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Drospirenone RS.*

In-Process Revision

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: The 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.*

Melting range, *Class 1* ⟨741⟩: between 198° and 203°. [NOTE—Dry over silica gel for not less than 24 hours prior to testing.]

Specific rotation ⟨781S⟩**:** between –186° and –196°.

Water, *Method I* ⟨921⟩**:** not more than 0.2%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Solvent—Use dimethylformamide.

Limit of 1,2-dimethoxyethane and diisopropyl ether—

Standard solution—Prepare a solution of 1,2-dimethoxyethane and diisopropyl ether in dimethylformamide to obtain a solution having known concentrations of about 0.1 mg and 0.05 mg per mL, respectively.

Test solution—Dissolve an accurately weighed portion of Drospirenone in dimethylformamide to obtain a solution having a known concentration of about 50 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.25-mm × 30-m capillary column coated with a 1.4-µm film of liquid phase G43. The column temperature is programmed according to the following steps: it is held at 40° for 10 minutes, then increased at a rate of 5° per minute to 70°; it is then increased at a rate of 30° per minute to 220°. The injection port temperature is maintained at 160°, and the detector temperature is maintained at 250°. The carrier gas is helium, flowing at a rate of about 32 ± 8 cm per second. [NOTE—For pressure-controlled systems, a column pressure of approximately 130 kPa will be necessary.] Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.6 for diisopropyl ether and 1.0 for 1,2-dimethoxyethane; and the relative standard deviation for six injections of the *Standard solution* is not more than 4.0%.

Procedure—Transfer 2.0 mL each of the *Test solution* and the *Standard solution* to separate headspace vials, and seal. The vials are maintained at 80° for 60 minutes prior to headspace injection. Record the chromatograms, and measure the peak areas for the 1,2-dimethoxyethane and diisopropyl ether peaks. Separately calculate the percentage of 1,2-dimethoxyethane and diisopropyl ether in the portion of Drospirenone 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 1,2-dimethoxyethane or diisopropyl ether in the *Standard solution;* C_U is the concentration, in mg per mL, of drospirenone in the *Test solution;* and r_U and r_S are the 1,2-dimethoxyethane or diisopropyl ether peak areas in the chromatograms obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.2% of 1,2-dimethoxyethane and 0.1% of diisopropyl ether are found.

Chromatographic purity—

Solvent A, Solvent B, Mobile phase, Diluent, Standard preparation, Assay preparation, and *Chromatographic system*—Proceed as described in the *Assay.*

Procedure—Separately inject equal volumes (about 10 L) of the *Standard preparation,* the *Assay preparation,* and the

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Diluting solution into the chromatograph, and record the chromatograms. Calculate the percentage of each impurity in the portion of Drospirenone taken by the formula:

$$100F(r_i / r_s),$$

in which F is the relative response factor equal to 1.3 for 15β,16β-methylene-3-oxo-4,6-pregnadiene-21,17-carbolactone with a relative retention time of 0.78, 0.5 for 15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone with a relative retention time of 0.73, and 1.0 for all other impurities; r_i is the peak area for each impurity; and r_s is the sum of the responses of all the peaks. Disregard peaks that are less than 0.05% of the drospirenone peak. Not more than 0.1% of any individual impurity is found; and not more than 0.4% of total impurities is found.

Assay—

Solvent A—Use water.

Solvent B— Use acetonitrile.

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

Diluent—Prepare a degassed mixture of water and acetonitrile (1 : 1).

Standard preparation—Dissolve accurately weighed quantities of USP Drospirenone RS in *Diluent* to obtain a solution having known concentrations of about 2 mg per mL.

Assay preparation—Transfer about 20 mg of drospirenone, accurately weighed, to a 10-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 245-nm detector and a 4.0-mm × 25-cm column containing 5-µm packing L1 that is maintained at a constant temperature of about 30°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solvent A* (%)	*Solvent B* (%)	Elution
0–28.5	64	36	isocratic
28.5–45	64→10	36→90	linear gradient
45–45.5	10→0	90→100	linear gradient
45.5–52	0	100	isocratic
52–53	0→64	100→36	linear gradient
53–80	64	36	equilibration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 7000 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.0%. No peaks with a signal-to-noise ratio >10 should be present in the chromatogram of the *Diluting solution* between 5 and 45 minutes.

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 response for the drospirenone peak. Calculate the quantity, in mg, of $C_{24}H_{30}O_3$ in the portion of Drospirenone taken by the formula:

$$10C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Drospirenone 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 (*USP29*)

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BRIEFING

Egg Phospholipids, page 401 of *PF* 29(2) [Mar.–Apr. 2003]. On the basis of comments received, it is proposed to change the Definition to reflect the various compositions of egg phospholipids in available products. It is also proposed to revise the limits in the tests for *Acid value* and *Peroxide value.*

(PPI: J. Kelly) RTS—41300-1

Add the following:

■Egg Phospholipids

» ~~Egg Phospholipids is a mixture of occurring phospholipids obtained from the yolk of hens' eggs and is suitable for use as an emulsifying agent in injectable emulsions. It contains not less than 60 percent (w/w) of phosphatidylcholine and not less than 5.0 percent (w/w) of phosphatidylethanolamine. The mixture may also contain not more than 3 percent (w/w) of sphingomyelin. It may also contain other related phospholipids. It may contain not more than 0.2 percent (w/w) DL-α-tocopherol when added as a preservative.~~ Egg Phospholipids is a mixture of naturally occurring phospholipids obtained from the yolk of hens' eggs, which is suitable for use as an emulsifying agent in injectable emulsions. The contents of phosphatidylcholine, phosphatidylethanolamine, and other related phospholipids are indicated in the labeling. It may also contain a suitable stabilizer.

Packaging and storage—Preserve under nitrogen in a sealed container, and store at a temperature of –10° or below.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Phosphatidylcholine RS. USP Phosphatidylethanolamine RS.* ~~*USP Sphingomyelin RS.*~~

Acid value ⟨401⟩**:** not more than ~~4.5.~~ 3.0.

Peroxide value ⟨401⟩**:** not more than ~~10.~~ 20.

Microbial limits ⟨61⟩—It meets the requirements of the test for absence of *Salmonella* species and *Escherichia coli.* The total ~~aerobic~~ microbial count does not exceed 100 cfu per g.

Bacterial endotoxins ⟨85⟩—It contains not more than 20 USP Endotoxin Units per g.

Water, *Method I* ⟨921⟩—Dissolve about 2 g, accurately weighed, in 50 mL of anhydrous methyl alcohol. Protect from atmospheric moisture during transfer. Determine the water content titrimetrically, using an accurately measured portion of this solution: not more that 6.0% is found.

Limit of nonphosphatidyl lipids—

Solvent: a mixture of chloroform and methyl alcohol (9 : 1).

Chromatographic column—Transfer 125 g of silica gel having an average pore size of 6 nm into a 600-mL beaker. [NOTE—Silica gel containing between 3% and 5% of moisture volatiles when heated at 200° has been found to be suitable.] Prepare a slurry with 400 mL of *Solvent,* and transfer to a 4.5-cm chromatographic column (see *Column Chromatography* under *Chromatography* ⟨621⟩). Drain the *Solvent* through the column to a level of about 1 cm above the silica gel bed. Place a plug of glass wool on top of the bed. Rinse the beaker and the column walls with 400 mL of *Solvent,* and drain to about 0.5 cm above the silica gel. Discard the eluted rinses, and place a suitable flask beneath the column.

Test solution—Transfer about 10 g of Egg Phospholipids, accurately weighed, to a 150-mL beaker, add 50 mL of *Solvent,* and mix to dissolve.

Procedure—Transfer the *Test solution* to the *Chromatographic column,* and drain to about 0.5 cm above the silica gel at a rate of about 8 to 10 mL per minute. Rinse the column containing the *Test solution* with three 20-mL portions of *Solvent,* allowing each rinse to pass through the column before adding the next. Add additional *Solvent* onto the column until 800 mL of eluate has been collected. Evaporate the eluate in a tared round-bottom, 250-mL flask to dryness, using a suitable rotary evaporator and a water bath maintained between 50° and 60°. If silica gel is visible after evaporation, redissolve the residue in *Solvent,* filter through a sintered-glass, medium-porosity funnel, wash the funnel with 25 mL of *Solvent,* transfer back to the round-bottom flask, and evaporate to dryness. Place the flask in a vacuum oven at about 55° for 1 hour. Transfer to a desiccator for not less than 1 hour, then weigh again. Repeat until the weight is constant within 1 mg. Calculate the gain in weight: not more than 5% of the weight of the Egg Phospholipids taken is found.

Content of phospholipids—

Solution A—Use filtered and degassed isopropyl alcohol.

Solution B—Use filtered and degassed hexane.

Solution C—Use filtered and degassed water.

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

Solvent—Prepare a mixture of isopropyl alcohol, hexane, and water (1 : 1 : 1).

Standard solutions—Transfer accurately weighed quantities of USP Phosphatidylcholine RS and USP Phosphatidylethanolamine RS~~, and USP Sphingomyelin RS~~ to separate flasks, dissolve each in *Solvent,* and dilute quantitatively and stepwise, if necessary, with *Solvent* to obtain *Standard solutions* having known concentrations of about 6 mg per mL, 1 mg per mL, and 0.5 mg per mL, respectively.

Test solution—Transfer about 1 g of Egg Phospholipids, accurately weighed, to a 100-mL volumetric flask, add 50 mL of *Solvent,* and mix. Dilute with *Solvent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an evaporative light-scattering detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at a constant temperature of about 25°. [NOTE—The parameters of detector operation may be adjusted to achieve an appropriate signal-to-noise ratio.] The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0	58	40	2	equilibration
0–7	58→52	40	2→8	linear gradient
7–15	52	40	8	isocratic

Chromatograph the *Standard solutions,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.6 for phosphatidylethanolamine and 1.0 for phosphatidylcholine~~, and 1.2 for sphingomyelin~~; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and identify the peaks of the relevant analytes in the chromatogram of the *Test solution* by comparison with the chromatograms obtained from the *Standard solutions.* Measure the

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areas of the analyte peaks. Plot the logarithms of the relevant responses versus the logarithms of the concentrations, in mg per mL, of each analyte obtained from the *Standard solutions,* and determine the regression line using a least-squares analysis. The correlation coefficient for the regression line is not less than 0.995. From the graphs so obtained, determine the concentration, *C,* in mg per mL, of the relevant analyte in the *Test solution.* Separately calculate the percentages of phosphatidylethanolamine and phosphatidylcholine~~, and sphingomyelin~~ in the portion of Egg Phospholipids taken by the formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of the USP Reference Standard in the relevant *Standard solution; W* is the weight, in g, of Egg Phospholipids taken to prepare the *Test solution;* and r_U and r_S are the peak areas of the relevant analytes in the chromatograms obtained from the *Test solution* and the *Standard solution,* respectively. ■1S (*USP29*)

BRIEFING

Multiple Electrolytes Injection Type 2, *USP 28* page 717 and page 3220 of the *First Supplement*—See briefing under *Anticoagulant Sodium Citrate Solution*.

(PA1: K. Russo; D. Bempong) RTS—42196-10

Change to read:

USP Reference standards ⟨11⟩—

■*USP Citric Acid RS.* ■1S (*USP29*)
USP Endotoxin RS. USP Sodium Lactate RS.

(Official April 1, 2009)

Change to read:

Assay for citrate *(if present)*—

~~*Mobile phase*—Prepare a filtered and degassed solution of 0.05 N sulfuric acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparations*—Dissolve an accurately weighed quantity of anhydrous sodium citrate, previously dried at 180° for 18 hours, in water to obtain a stock solution having a known concentration of about 10 mg per mL. Dilute accurately measured volumes of this stock solution quantitatively with water to obtain three *Standard preparations* having known concentrations of about 0.5, 1.0, and 2.0 mg, respectively, of anhydrous sodium citrate per mL.~~

~~*Assay preparation*—Where the labeled quantity is greater than 10 mEq of citrate per liter, dilute an accurately measured volume of Injection quantitatively with water to obtain a solution containing about 0.01 mEq of citrate per mL. Where the labeled quantity is 10 mEq of citrate or less per liter, use the undiluted Injection as the *Assay preparation.*~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector, a 7.8-mm × 4-cm guard column containing packing L17, and a 7.8-mm × 30-cm analytical column containing packing L17, and is maintained at about 60°. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard preparation* containing 1 mg of anhydrous sodium citrate per mL, 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 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparations* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Plot the responses of the *Standard preparations* versus concentration, in mg of anhydrous sodium citrate per mL, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, *C,* in mg of anhydrous sodium citrate equivalent per mL, in the *Assay preparation.* Calculate the quantity, in mEq per liter, of citrate ($C_6H_8O_7$) in the Injection taken by the formula:~~

~~$$(C/258.07)(L/D),$$~~

~~in which 258.07 is the molecular weight of anhydrous sodium citrate, *L* is the labeled quantity, in mEq per liter, of citrate in the Injection, and *D* is the quantity, in mEq per mL, of citrate in the *Assay preparation,* based on the labeled quantity and the extent of dilution.~~

■*Mobile Phase* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Standard preparation—Dissolve an accurately weighed quantity of USP Citric Acid RS in freshly prepared 1 mM sodium hydroxide to obtain a solution having a known concentration of about 0.3 mEq of citrate ($C_6H_5O_7$) per L.

Assay preparation—Dilute an accurately measured volume of Injection quantitatively with freshly prepared sodium hydroxide to obtain a solution having a concentration of about 0.3 mEq of citrate per L in 1 mM sodium hydroxide.

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Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, calculate the quantity, in mEq per L, of citrate ($C_6H_5O_7$) in the Injection taken by the formula:

$$C_S D(r_U / r_S),$$

in which C_S is the concentration, in mEq per L, of citrate in the *Standard preparation; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S *(USP29)*

(Official April 1, 2009)

BRIEFING

Multiple Electrolytes and Dextrose Injection Type 2, *USP 28* page 720 and page 3221 of the *First Supplement*—See briefing under *Anticoagulant Sodium Citrate Solution*.

(PA1: K. Russo; D. Bempong) RTS—42196-11

Change to read:

USP Reference standards ⟨11⟩—

■*USP Citric Acid RS.*■1S *(USP29)*
USP Endotoxin RS. USP Potassium Gluconate RS. USP Sodium Lactate RS.

(Official April 1, 2009)

Change to read:

Assay for citrate *(if present)*—

~~*Mobile phase, Standard preparations,* and *Chromatographic system*—Prepare as directed in the *Assay for citrate* under *Multiple Electrolytes Injection Type 2.*~~

~~*Assay preparation*—Where the labeled quantity is greater than 10 mEq of citrate per liter, dilute an accurately measured volume of Injection quantitatively with water to obtain a solution containing about 0.01 mEq of citrate per mL. Where the labeled quantity is 10 mEq or less per liter, use the undiluted Injection as the *Assay preparation.*~~

~~*Procedure*—Proceed as directed for *Procedure* in the *Assay for citrate* under *Multiple Electrolytes Injection Type 2.* Calculate the quantity, in mEq per liter, of citrate ($C_6H_5O_7$) in the Injection taken by the formula:~~

~~$$(C / 258.07)(L / D),$$~~

~~in which the terms are as defined therein.~~

■*Mobile Phase* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Standard preparation—Dissolve an accurately weighed quantity of USP Citric Acid RS in freshly prepared 1 mM sodium hydroxide to obtain a solution having a known concentration of about 0.3 mEq of citrate ($C_6H_5O_7$) per L.

Assay preparation—Dilute an accurately measured volume of Injection quantitatively with freshly prepared sodium hydroxide to obtain a solution having a concentration of about 0.3 mEq of citrate per L in 1mM sodium hydroxide.

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, calculate the quantity, in mEq per L, of citrate ($C_6H_5O_7$) in the portion of Injection taken by the formula:

$$C_S D(r_U / r_S),$$

in which C_S is the concentration, in mEq per L, of citrate in the *Standard preparation; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S *(USP29)*

(Official April 1, 2009)

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BRIEFING

Enoxaparin Sodium Injection, page 1882 of *PF* 29(6) [Nov.–Dec. 2003]. It is proposed to correct the designation of the column used in the *Free sulfate content* test in this new monograph.

(HDQ: M. Marques) RTS—42324

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.

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, ~~pre-packed with L## and L## packings~~ both containing L61 packing (see *Chromatography* ⟨621⟩), 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 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:

$$T \times M_S / 10m,$$

[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.

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*.■1S (*USP29*)

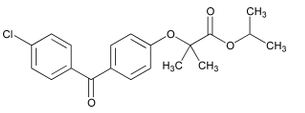
BRIEFING

Fenofibrate. 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 procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Lichrospher RP 18e brand of L1 column. The typical retention time for fenofibrate is about 13 minutes.

(PA4: E. Gonikberg; NL: L. Paul; PSD: C. Okeke) RTS—42290-1

Add the following:

■Fenofibrate



$C_{20}H_{21}ClO_4$ 360.83

Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoate [*49562-28-9*].

» Fenofibrate contains not less than 98.5 percent and not more than 101.0 percent of $C_{20}H_{21}ClO_4$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers. Store at room temperature.

USP Reference standards ⟨11⟩**—***USP Fenofibrate RS. USP Fenofibrate Related Compound A RS. USP Fenofibrate Related Compound B RS. USP Fenofibrate Related Compound C RS.*

Color of solution ⟨631⟩**—**

Reference solution—Mix 5 mL of *Matching Fluid G* and 95 mL of dilute hydrochloric acid (1 in 40).

Test solution—Transfer 500 mg of Fenofibrate to a 10-mL volumetric flask, dissolve in and dilute with acetone to volume, and mix.

Procedure—Proceed as directed under *Color and Achromicity* ⟨631⟩: the *Test solution* is clear and not more intensely colored than the *Reference solution*.

Identification—*Infrared Absorption* ⟨197K⟩.

Melting range, *Class 1a* ⟨741⟩**:** between 79° and 82°.

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Acidity—Dissolve 1.0 g in 50 mL of alcohol previously neutralized to phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS: not more than 0.2 mL of 0.1 N sodium hydroxide VS is required to change the color of the indicator to pink.

Loss on drying ⟨731⟩**—**Dry it in vacuum over phosphorus pentoxide at 60° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%, determined on 1.0 g.

Chloride ⟨221⟩**—**

Test solution—Add 25 mL of water to 5.0 g of Fenofibrate, and heat at 50° for 10 minutes. Cool, dilute with water to 50.0 mL, filter, and use the filtrate. [NOTE—Retain the remaining portion of the *Test solution* for the test for *Sulfate*.]

Procedure—Use 10 mL of the *Test solution*: it shows no more chloride than corresponds to 0.15 mL of 0.020 N hydrochloric acid (0.01%).

Sulfate ⟨221⟩**—**Use 10 mL of the *Test solution* retained from the test for *Chloride*: it shows no more sulfate than corresponds to 0.15 mL of 0.020 N sulfuric acid (0.01%).

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Mobile phase—Proceed as directed in the *Assay.*

Impurity standard solution—Dissolve accurately weighed quantities of USP Fenofibrate RS, USP Fenofibrate Related Compound A RS, USP Fenofibrate Related Compound B RS, and USP Fenofibrate Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 1 µg per mL each of fenofibrate, fenofibrate related compound A, and fenofibrate related compound B, and about 2 µg per mL of fenofibrate related compound C.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*. In addition, chromatograph the *Impurity standard solution*, and record the peak responses as directed for *Procedure*: the resolution, *R,* between fenofibrate related compound A and fenofibrate related compound B is not less than 1.5.

Procedure—Separately inject equal volumes (about 20 µL) of the *Impurity standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the fenofibrate peak and the peaks due to the impurities and degradation products listed in *Table 1*. Measure the responses for the major peaks, and calculate the percentage of each of fenofibrate related compound A, fenofibrate related compound B, and fenofibrate related compound C in the portion of Fenofibrate taken by the formula:

$$10C/W(r_U/r_S),$$

in which C is the concentration, in µg per mL, of the appropriate fenofibrate related compound in the *Impurity standard solution; W* is the weight, in mg, of fenofibrate taken to prepare the *Test solution;* and r_U and r_S are the peak responses of the appropriate fenofibrate related compound obtained from the *Test solution* and the *Impurity standard solution,* respectively.

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Table 1

Name	Relative Retention Time	Limit (%)
(4-Chlorophenyl)(4-hydroxyphenyl)methanone[1]	0.34	0.1
2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid (fenofibric acid)[2]	0.36	0.1
(3*RS*)-3-[4-(4-Chlorobenzoyl)phenoxy]butan-2-one	0.50	0.1
Methyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoate	0.65	0.1
Ethyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoate	0.80	0.1
(4-Chlorophenyl)[4-(1-methylethoxy)phenyl]methanone	0.85	0.1
1-Methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate[3]	1.35	0.2
Any other impurity	—	0.1

[1] Fenofibrate related compound A
[2] Fenofibrate related compound B
[3] Fenofibrate related compound C

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

$$10C/W(r_U/r_S),$$

in which C is the concentration, in µg per mL, of fenofibrate in the *Impurity standard solution; W* is as defined above; r_U is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response of fenofibrate obtained from the *Impurity standard solution.* In addition to not exceeding the limits for each impurity in *Table 1*, not more than 0.5% of total impurities is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water acidified with phosphoric acid to a pH of 2.5 (70: 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Fenofibrate 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.

Assay preparation—Transfer about 100 mg of Fenofibrate, 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 286-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromato-

graph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six replicate injections is not more than 1.0%.

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 responses for the major peaks. Calculate the quantity, in mg, of $C_{20}H_{21}ClO_4$ in the portion of Fenofibrate taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Fenofibrate 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 (*USP29*)

BRIEFING

Flurazepam Hydrochloride, *USP 28* page 864 and page 3232 of the *First Supplement.* In stating the limits in *Identification* test *B,* it is proposed to calculate the absorptivities on the anhydrous rather than on the dried basis.

(PA3: R. Ravichandran) RTS—42304-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—[NOTE—Do not grind excessively, as decomposition may occur.]

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 10 µg per mL.

Medium: sulfuric acid in methanol (1 in 36).

Absorptivities at 239 nm, calculated on the ~~dried~~ ■anhydrous■1S (*USP29*) basis, do not differ by more than 3.0%.

C: Prepare a solution of it in methanol containing 3 mg per mL. Apply 10 µL of this solution and 10 µL of a methanol solution of USP Flurazepam Hydrochloride RS containing 3 mg per mL to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of ethyl acetate and ammonium hydroxide (200 : 1) 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 viewing under short-wavelength UV light: the R_F value of the principal spot in the chromatogram of the test solution corresponds to that obtained from the solution of the Reference Standard.

D: To 2 mL of a solution (1 in 20), add 1 mL of 2 N nitric acid: the solution responds to the tests for *Chloride* ⟨191⟩, 5 drops of silver nitrate TS being used.

BRIEFING

Glutaral Concentrate, *USP 28* page 909. It is proposed to slightly modify the lower limit of the test for *Specific gravity* to accommodate variation in the manufacturing process for this product.

(PA7: B. Davani) RTS—41889-1

Change to read:

Specific gravity ⟨841⟩**:** between ~~1.128~~ ■1.126■1S (*USP29*) and 1.135 at ~~20°/20°.~~ ■20°.■1S (*USP29*)

BRIEFING

Glyburide and Metformin Hydrochloride Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the tests for *Related compounds—glyburide* and *Dissolution* and in the *Assay for glyburide* are based on analyses performed with the Zorbax-Rx C8 brand of L7 column. The typical retention time for the glyburide peak is about 14 minutes. The liquid chromatographic procedures in the test for *Chromatographic purity—metformin hydrochloride*

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and in the *Assay for metformin hydrochloride* are based on analyses performed with the µBondapak C18 brand of L1 column. The typical retention time for the metformin peak is about 7.5 minutes.

(PA4: E. Gonikberg; BPC: M. Marques; NL: W. Paul; PSD: C. Okeke) RTS—41684-1

Add the following:

■Glyburide and Metformin Hydrochloride Tablets

» Glyburide and Metformin Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of glyburide ($C_{23}H_{28}ClN_3O_5S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Glyburide RS. USP Glyburide Related Compound A RS. USP Metformin Hydrochloride RS. USP Metformin Related Compound B RS. USP Metformin Related Compound C RS.*

Identification—

A: GLYBURIDE—

Infrared Absorption⟨197K⟩—Prepare the test specimen as follows. Grind 5 tablets to a fine powder. Add 25 mL of water, and shake for 5 minutes. Add 25 mL of chloroform, and shake for an additional 5 minutes. Centrifuge at 2500 rpm for 5 minutes. Transfer the lower chloroform layer to another container, evaporate the solvent under a stream of nitrogen, and dry the extract at 60° for 3 hours: the IR absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Glyburide RS.

B: METFORMIN HYDROCHLORIDE—

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 for metformin hydrochloride.*

Dissolution ⟨711⟩**—**

GLYBURIDE—

Medium: 0.05 M boric acid and 0.05 M potassium chloride solution, prepared by dissolving 3.09 g of boric acid and 3.73 g of potassium chloride in approximately 250 mL of water, adjusting with 1 N sodium hydroxide to a pH of 9.5, and diluting with water to 1 L; 500 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of glyburide ($C_{23}H_{28}ClN_3O_5S$) dissolved by employing the following method.

Phosphate buffer—Dissolve 28.7 g of monobasic ammonium phosphate in water, and dilute with water to 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (1 : 1), and adjust with 1 N sodium hydroxide to a pH of 5.3. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 10 mg of USP Glyburide RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 20 mL of acetonitrile, and dilute with *Medium* to volume. Dilute further with *Medium* to obtain a solution having a glyburide concentration, in mg per mL, of *L*/500, where *L* is the label claim, in mg, of glyburide.

Test solution—Pass a portion of the solution under test through a 0.45-µm polypropylene filter or a 1-µm glass fiber filter.

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 5-µm packing L7. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is between 0.8 and 2.0; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the glyburide peaks. Calculate the quantity of glyburide dissolved, expressed as a percentage of the glyburide label claim, by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times L},$$

in which r_U and r_S are the peak responses for the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg, of glyburide.

Tolerances—Not less than 85% (Q) of the labeled amount of glyburide is dissolved in 30 minutes.

METFORMIN HYDROCHLORIDE—

Medium: 0.05 M phosphate buffer, pH 6.8, prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 1000 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by employing the following method.

Standard solution—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Medium*. Dilute with *Medium*, if necessary, to obtain a solution having a concentration, in mg per mL, of metformin hydrochloride of about L/1000, where L is the label claim, in mg, of metformin hydrochloride.

Test solution—Pass a portion of the solution under test through a 0.45-µm polypropylene filter or a 1-µm glass fiber filter.

Procedure—Determine the amount of metformin hydrochloride dissolved by employing UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the *Test solution* in comparison with the *Standard solution*. Calculate the percentage of metformin hydrochloride dissolved, expressed as a percentage of the metformin hydrochloride label claim, by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times L},$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Tolerances—Not less than 85% (Q) of the labeled amount of metformin hydrochloride is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Weight variation* for metformin hydrochloride and for *Content uniformity* for glyburide.

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Related compounds—

GLYBURIDE—

Diluent, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay for glyburide*.

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

Standard solution—Transfer 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for glyburide*.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of glyburide related compound A in the portion of Tablets taken by the formula:

$$100CFVD(r_i / r_S)/NL,$$

in which C is the concentration, in mg per mL, of glyburide in the *Standard solution; F* is the relative response factor of glyburide related compound A and is equal to 0.8; V is the volume in which the sample is dissolved to prepare the *Test solution; D* is any further dilution of the sample; r_i is the peak response for glyburide related compound A in the *Test solution;* r_S is the peak response for glyburide in the *Standard solution; N* is the number of Tablets taken to prepare the *Test solution;* and L is the glyburide label claim in mg per Tablet: not more than 1.0% is found.

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

$$100CVD(r_i / r_S)/NL,$$

in which r_i is the peak response for each impurity obtained from the *Test solution,* and the other terms are as defined above: not more than 0.2% of any other impurity is found; and the sum of all impurities, excluding glyburide related compound A, is not more than 0.50%. Disregard any peak less than 0.05% and also disregard any peak observed in the blank.

Chromatographic purity—

METFORMIN HYDROCHLORIDE—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay for metformin hydrochloride*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for metformin hydrochloride.*

Procedure—Inject a volume (about 5 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all 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 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found. Disregard any peak less than 0.05%, and disregard any peak observed in the blank.

Assay for glyburide—

Ammonium phosphate buffer solution—Dissolve 28.8 g of monobasic ammonium phosphate in water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of *Ammonium phosphate buffer solution* and acetonitrile (60 : 40), and adjust with 1 N sodium hydroxide solution to a pH of 5.3. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Use a mixture of acetonitrile and water (50 : 50).

Standard preparation—Transfer an accurately weighed quantity of USP Glyburide RS to a suitable volumetric flask. Dissolve first in acetonitrile, using 50% of the final volume, then dilute with water to volume, and mix, to obtain a solution having a known concentration of about 0.25 mg of glyburide per mL. Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.025 mg per mL.

System suitability intermediate preparation—Prepare a solution of USP Glyburide Related Compound A RS in *Diluent* having a concentration of 0.025 mg per mL. Transfer 50 µL of this solution to a 50-mL volumetric flask, and dilute with *Standard preparation* to volume.

System suitability preparation—Transfer an accurately weighed quantity of USP Metformin Hydrochloride RS, and dilute quantitatively with the *System suitability intermediate preparation* to obtain a solution having a known concentration of about 5.0 mg per mL.

Assay preparation—Dissolve not fewer than 5 Tablets in *Diluent* by stirring with a magnetic stirring bar for at least 1 hour. Dilute accurately, and stepwise, if necessary, to obtain a solution having a glyburide concentration of approximately 0.025 mg per mL, based on the label claim. Centrifuge a portion of this solution at 3000 rpm for 10 minutes, and use the clear supernatant. [NOTE—Retain a portion of the solution for the *Assay for metformin hydrochloride.*]

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 5-µm packing L7. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure*: for the peak due to glyburide, the capacity factor, k', is not less than 7; the column efficiency is not less than 3000 theoretical plates; and the relative standard deviation for replicate injections is not more than 1.5%. For the peak due to glyburide related compound A, the relative retention time is approximately 0.30 with respect to glyburide; and the relative standard deviation for replicate injections is not more than 10%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for about 1.25 times the retention time of the glyburide peak, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of glyburide ($C_{23}H_{28}ClN_3O_5S$) by the formula:

$$CVD(r_U / r_S)/N,$$

in which C is the concentration, in mg per mL, of USP Glyburide RS in the *Standard preparation; V* is the volume, in mL, used to prepare the *Assay preparation; D* is the dilution factor of the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and N is the number of Tablets used to prepare the *Assay preparation.*

Assay for metformin hydrochloride—

Buffer solution—Transfer 1.0 g each of sodium heptanesulfonate and sodium chloride to a 2000-mL volumetric flask, add 1800 mL of water, and mix. Adjust with 0.06 M phosphoric acid to a pH of 3.85, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Use a 2.5% solution of acetonitrile in water.

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with

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Diluent to obtain a solution having a known concentration of about 0.25 mg per mL. Use sonication if necessary to achieve a complete dissolution.

System suitability preparation—Dissolve suitable quantities of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent* to obtain a solution containing about 25 µg of each per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay preparation—Quantitatively dilute a portion of the *Assay preparation,* obtained as directed for *Assay for glyburide,* with water to obtain a solution having an expected concentration of about 0.25 mg of metformin hydrochloride per mL, based on the label claim.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.86 for metformin related compound B, 1.0 for metformin, and about 2.1 to 2.3 for metformin related compound C [NOTE—This impurity can have a variable retention time]; the resolution, *R,* between metformin related compound B and metformin is not less than 1.5; the tailing factor for the metformin peak is not less than 0.8 and not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5% for the metformin peak and not more than 10% for each of the peaks due to metformin related compound B and metformin related compound C.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms until after the elution locus of metformin related compound C; and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$CVD(r_U / r_S)/N,$$

in which C is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, used to prepare the *Assay preparation; D* is the dilution factor of the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and N is the number of Tablets used to prepare the *Assay preparation.* ■1S (*USP29*)

BRIEFING

Hypromellose Ophthalmic Solution, *USP 28* page 990 and page 3246 of the *First Supplement.* It is proposed to remove references to the *Hypromellose* monograph, in preparation for revising the *Hypromellose* monograph with changes resulting from the harmonization process.

(EMC: J. Lane) RTS—42401-1

Change to read:

Identification—

A: ~~It meets the requirements of *Identification* test *C* under *Hypromellose.*~~

■Pour a few mL of Ophthalmic Solution onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results. ■1S (*USP29*)

B: Heat 5 mL of Ophthalmic Solution in a test tube over a low flame: the warm solution turns cloudy but clears upon chilling.

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BRIEFING

Ketoprofen, *USP 28* page 1099. To provide the needed accuracy for potency determination, it is proposed to change the procedure in the *Assay* by increasing the sample weight from 200 to 450 mg.

(PA2: C. Anthony) RTS—42292-1

Change to read:

Assay—Dissolve about ~~200 mg~~

■450 mg■1S (*USP29*)
of Ketoprofen, accurately weighed, in 25 mL of alcohol. Add 25 mL of water and several drops of phenol red TS, and titrate with 0.1 N sodium hydroxide having been standardized by a similar titration of primary standard benzoic acid. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 25.43 mg of $C_{16}H_{14}O_3$.

BRIEFING

Metformin Hydrochloride Extended-Release Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the test for *Chromatographic purity* and in the *Assay* are based on analyses performed with the µBondapak C18 brand of L1 column. The typical retention time for metformin is about 7.5 minutes.

(PA4: E. Gonikberg; BPC: M. Marques; NL: L. Paul; PSD: C. Okeke) RTS—41431-1; 41431-2; 41008-2; 42250-1; 42232-1; 42207-2; 42374-1

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Add the following:

■Metformin Hydrochloride Extended-Release Tablets

» Metformin Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed, light-resistant containers, and 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. USP Metformin Related Compound B RS. USP Metformin Related Compound C 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⟩—

TEST 1—

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 1000 mL.

Apparatus 2: 100 rpm, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*.

Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, amount dissolved	750-mg Tablet, amount dissolved
1	between 20% and 40%	between 22% and 42%
3	between 45% and 65%	between 49% and 69%
10	not less than 85%	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that the product meets *USP Dissolution Test 2*.

Medium: Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 2, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formula:

$$\frac{A_U \times C_s \times D_U}{A_s}$$

in which A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; C_S is the concentration of metformin hydrochloride, in mg per mL, in the Standard solution; and D_U is the dilution factor of the solution under test. Calculate the percentage of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at each time point by the following formulas:

Percentage dissolved at the first time point (1 hour):

$$\frac{C_1 \times 1000 \times 100}{L}$$

in which C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the first time interval; 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Percentage dissolved at the second time point (2 hours):

$$\frac{C_2 \times (1000 - SV_1) + C_1 \times SV_1 \times 100}{L}$$

in which C_2 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the second time interval; 1000 is the volume, in mL, of *Medium; SV_1* is the volume, in mL, of the sample withdrawn at 1 hour; C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at 1 hour; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Percentage dissolved at the *n*th time point:

$$\frac{C_n \times [1000 - (n-1)SV] + (C_1 + C_2 + ... + C_{n-1}) \times SV \times 100}{L}$$

in which C_n is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the *n*th time interval; n is the time interval of interest; SV is the volume, in mL, of sample withdrawn at each time interval; C_1, C_2, C_3, ... C_{n-1} is the content of metformin hydrochloride, in mg per mL, in the *Medium* at each time interval; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
6	between 65% and 85%
10	not less than 85%

TEST 3—If the product complies with this test, the labeling indicates that the product meets *USP Dissolution Test 3*.

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1*.

Times: 1, 2, 5, and 12 hours for Tablets labeled to contain 500 mg; and 1, 3, and 10 hours for Tablets labeled to contain 750 mg.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{300} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution, A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{120} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; C_{300} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 5 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

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Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 500 MG

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
5	between 60% and 80%
12	not less than 85%

FOR TABLETS LABELED TO CONTAIN 750 MG

Time (hours)	Amount dissolved
1	between 22% and 42%
3	between 49% and 69%
10	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that the product meets *USP Dissolution Test 4*.

Medium: Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 3, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm (shoulder) on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formulas specified in *Test 2.*

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 20% and 40%
3	between 45% and 65%
6	between 65% and 85%
10	not less than 85%

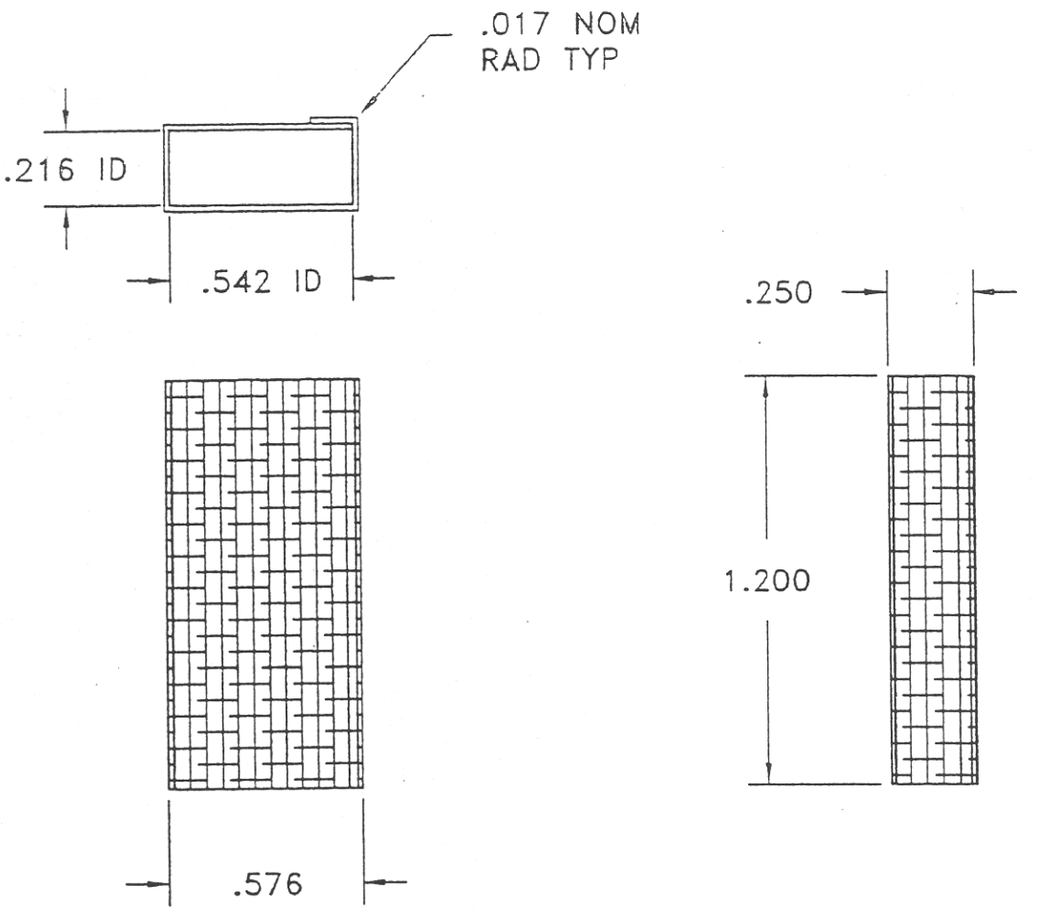
TEST 5—If the product complies with this test, the labeling indicates that the product meets *USP Dissolution Test 5.*

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 900 mL, deaerated.

Apparatus 1: 100 rpm, with the vertical holder described below.

Times: 2, 8, and 16 hours.

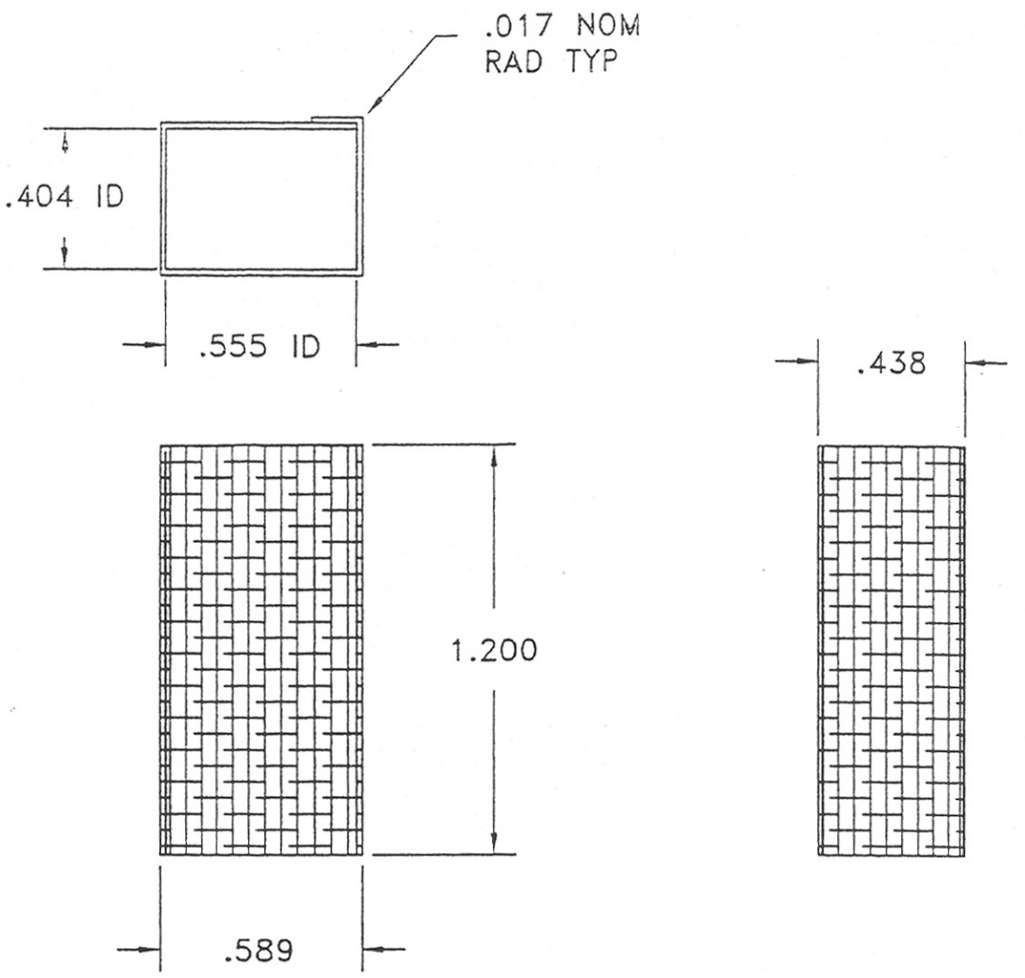
Procedure—Place a vertical sample holder into each basket (see *Figures 1* and *2*). Place one Tablet inside the sample holder, making sure that the Tablets are vertical at the bottom of the baskets. Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formulas specified in *Test 2.*



NOTES:

1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. TOLERANCES TO BE +/-.010

Figure 1



NOTES:

1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. TOLERANCES TO BE +/-.010

Figure 2

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, amount dissolved	1000-mg Tablet, amount dissolved
2	not more than 30%	not more than 30%
8	between 60% and 85%	between 65% and 90%
16	not less than 90%	not less than 90%

TEST 6—If the product complies with this test, the labeling indicates that the product meets *USP Dissolution Test 6.*

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.05; 1000 mL, deaerated.

Apparatus 2: 100 rpm, with USP sinker.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; C_{600} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, amount dissolved	750-mg Tablet, amount dissolved
1	between 20% and 40%	between 20% and 40%
3	between 45% and 65%	between 45% and 65%
10	not less than 85%	not less than 85%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Chromatographic purity—

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

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

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 each impurity in the portion of Tablets 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 the peaks: not more than 0.1% of any individual impurity is found, and not more than 0.5% of total impurities is found. Disregard any peak less than 0.05%, and disregard any peak observed in the blank.

Assay—

Buffer solution—Transfer 1.0 g each of sodium heptanesulfonate and sodium chloride to a 2000-mL volumetric flask, add 1800 mL of water, and mix. Adjust with 0.06 M phosphoric acid to a pH of 3.85, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Use a 1.25% solution of acetonitrile in water.

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about (*L*/4000) mg per mL, where *L* is the labeled quantity, in mg, of metformin hydrochloride in each Tablet.

System suitability preparation—Dissolve suitable quantities of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent* to obtain a solution containing about 12.5 µg of each per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay stock preparation—Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed portion of the powder, equivalent to the average Tablet weight, to a homogenization vessel, and accurately add 500 mL of 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized.

Assay preparation—Pass a portion of the *Assay stock preparation* through a filter having a 0.45-µm porosity, discarding the first 3 mL of filtrate. Transfer 25 mL of the filtrate to a 200-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.86 for metformin related compound B, 1.0 for metformin, and about 2.1 to 2.3 for metformin related compound C [NOTE—This impurity can have a variable retention time]; the resolution, *R,* between peaks due to metformin related compound B and to metformin is not less than 1.5; the tailing factor for the metformin peak is not less than 0.8 and not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5% for the metformin peak and not more than 10% for each of the peaks due to metformin related compound B and metformin related compound C.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, carrying out the run until after the elution locus of metformin related compound C; record the chromatograms; and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$C(V/W)TD(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of the *Assay stock preparation; W* is the

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weight, in mg, of sample used to prepare the *Assay stock preparation; T* is the average Tablet weight, in mg; *D* is the dilution factor of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

BRIEFING

Methylcellulose Ophthalmic Solution, *USP 28* page 1258; **Methylcellulose Oral Solution,** *USP 28* page 1258; **Methylcellulose Tablets,** *USP 28* page 1258. It is proposed to remove references to the *Methylcellulose* monograph, in preparation for revising the *Methylcellulose* monograph with changes resulting from the harmonization process.

(EMC: J. Lane) RTS—42400-3

Change to read:

Identification—~~It responds to *Identification* tests *B* and *C* under *Methylcellulose*.~~

■**A:** Heat a few mL of Ophthalmic Solution: the solution becomes cloudy and a flaky precipitate, which redissolves as the solution cools, appears.

B: Pour a few mL of Ophthalmic Solution onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.■1S (*USP29*)

BRIEFING

Methylcellulose Oral Solution, *USP 28* page 1258—See briefing under *Methylcellulose Ophthalmic Solution.*

(EMC: J. Lane) RTS—42400-2

Change to read:

Identification—~~It responds to *Identification* tests *B* and *C* under *Methylcellulose*.~~

■**A:** Heat a few mL of Oral Solution: the solution becomes cloudy and a flaky precipitate, which redissolves as the solution cools, appears.

B: Pour a few mL of Oral Solution onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.■1S (*USP29*)

BRIEFING

Methylcellulose Tablets, *USP 28* page 1258—See briefing under *Methylcellulose Ophthalmic Solution.*

(EMC: J. Lane) RTS—42400-1

Change to read:

Identification—~~Add the residue obtained in the *Assay* to 50 mL of water: the solution responds to the *Identification* tests under *Methylcellulose*.~~

■**A:** Gently add about 250 mg of the residue obtained in the *Assay* to the top of 25 mL of water in a beaker, and allow to disperse over the surface, tapping the top of the container to ensure an even dispersion of the test specimen. Allow the beaker to stand until the specimen becomes transparent and mucilaginous (about 5 hours), and swirl the beaker to wet

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the remaining substance, add a stirring bar, and stir until dissolved: the mixture remains stable when an equal volume of 1 N sodium hydroxide or 1 N hydrochloric acid is added.

B: Heat a few mL of the solution prepared for *Identification* test *A*: the solution becomes cloudy and a flaky precipitate, which redissolves as the solution cools, appears.

C: Pour a few mL of the solution prepared for *Identification* test *A* onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.■1S (*USP29*)

BRIEFING

Metronidazole Benzoate, *USP 28* page 1286. It is proposed to revise the test for *Related compounds* to lower the concentration of *Standard solution B* from 1.0% to 0.2%. In addition, it is proposed to specify the use of appropriate Reference Standards in *Standard solution C*. The *USP Reference standards* section is being revised to reflect this change.

(PA7b: B. Davani) RTS—42255-1

Change to read:

USP Reference standards ⟨11⟩—

■*USP Metronidazole RS.*■1S (*USP29*)
USP Metronidazole Benzoate RS.

■*USP Tinidazole Related Compound A RS.*■1S (*USP29*)

Change to read:

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~~

■USP Metronidazole RS and USP Tinidazole Related Compound A RS,■1S (*USP29*)
accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with acetone to volume, and mix.

■[NOTE—USP Tinidazole Related Compound A RS is 2-methyl-5-nitroimidazole.]■1S (*USP29*)

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~~

■tinidazole related compound A■1S (*USP29*)
spots obtained from *Standard solution C* are clearly separated; no

■secondary■1S (*USP29*)
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 the principal spot, obtained from the *Test solution* are larger or more intense than the principal spot obtained from *Standard solution B* ~~(1.0%)~~

■(0.2%).■1S (*USP29*)

BRIEFING

Oxandrolone Tablets, *USP 28* page 1427 and page 344 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to add a *Dissolution Test 2* for the recently approved generic version of this product. The chromatographic procedure in this test was validated using a Inertsil ODS(3) brand of L1 packing. Using this column, the retention time for oxandrolone is about 6.5 minutes. In the absence of any adverse comments, it is proposed to implement this revision via the *Fifth Interim Revision Announcement*, pertaining to *USP 28–NF 23*, with an official date of October 1, 2005.

(BPC: M. Marques) RTS—42295-1

Add the following:

•**Labeling**—When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* test used only if *Test 1* is not used.•5

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Change to read:

•**Dissolution** ⟨711⟩—

•TEST 1—•5

Medium: a solution of water and isopropanol (7 : 3); 500 mL.
Apparatus 2: 100 rpm.
Time: 60 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Internal standard solution—Dissolve accurately weighed quantities of 17α-methyl testosterone, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.2 mg per mL (for tablets with 2.5-mg label claim) and about 0.8 mg per mL (for tablets with 10-mg label claim).

Standard solution—Dissolve an accurately weighed quantity of USP Oxandrolone RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 1 mg per mL.

Working standard solution—Combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polytef filter. Transfer 20 mL of the filtrate to a separatory funnel, add 400 µL of the *Internal standard solution,* 40 mL of 10% potassium chloride solution, and 8 mL of chloroform. In separate separatory funnels, prepare an extraction blank and an internal standard blank in a similar manner using 20 mL of filtered *Medium* in place of the solution under test and excluding the *Internal standard solution* from the extraction blank. Shake each funnel, and allow the layers to separate. Collect the lower chloroform layer. Repeat the extraction procedure one more time. Evaporate the solvents under a stream of nitrogen at 45° until just dry. Reconstitute the dried residue with 2 mL of acetonitrile (for tablets with 2.5-mg label claim) or with 8 mL of acetonitrile (for tablets with 10-mg label claim), and sonicate for 10 minutes.

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 0.5-µm phase G27. The carrier gas is helium, flowing at a rate of about 16.8 mL per minute. The injection port and detector temperatures are maintained at 190° and 320°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is increased at a rate of 25° per minute to 280°, and maintained at 280° for 3 minutes. Then the column temperature is increased at a rate of 10° per minute to 320°, and maintained at 320° for 3 minutes. Chromatograph the acetonitrile, the extraction blank, and the internal standard blank, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5. Make two injections of the *Working standard solution,* and record the peak responses. The average oxandrolone/*Internal standard solution* peak area percent comparison is between 98.0% and 102.0%. The resolution, *R,* between the oxandrolone peak and the nearest eluting peak is equal to or greater than 1.5.

Procedure—Separately inject equal volumes (0.5 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 $C_{19}H_{30}O_3$ released by the formula:

$$\frac{C_S \times \text{sample ratio} \times V_{UF} \times 500 \times 100}{\text{Standard ratio} \times V_{UI} \times LC},$$

in which C_S is the concentration, in mg per mL, of oxandrolone in the *Standard solution;* sample ratio is the area ratio of oxandrolone to 17α-methyltestosterone in the sample injection for each *Test solution;* V_{UF} is the final volume, in mL, of the sample after reconstitution of the dry residue; 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; standard ratio is the mean area ratio of oxandrolone to 17α-methyltestosterone in all injections of the *Standard solution;* V_{UI} is the initial sample volume, in mL, used in the extraction; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of oxandrolone ($C_{19}H_{30}O_3$) is dissolved in 60 minutes.•2

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 1% polysorbate 80 in water; 500 mL, deaerated.

Apparatus 2: 100 rpm.

Time: 120 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 20 mg of USP Oxandrolone RS, accurately weighed, to a 200-mL volumetric flask. Add about 20 mL of acetonitrile, and sonicate to dissolve. Dilute with *Medium* to volume, and mix.

Working standard solution—Quantitatively dilute the *Standard stock solution* with *Medium* to obtain a solution having a final concentration of about 5 µg per mL for Tablets with a label claim of 2.5 mg, or a final concentration of about 20 µg per mL for Tablets with a label claim of 10 mg.

Test solution—Withdraw about 10 mL of the solution under test from the vessel. Centrifuge in a glass tube at 2000 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a reflective index detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the tailing fac-

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tor is not more than 2.0; the column efficiency is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{19}H_{30}O_3$ released by the formula:

$$\frac{r_U \times C_S \times D \times 500 \times 100}{r_S \times LC},$$

in which r_U and r_S are the peak responses for the *Test solution* and *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution; D* is the dilution factor of the *Test solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim in mg.

Tolerances—Not less than 65% *(Q)* of the labeled amount of $C_{19}H_{30}O_3$ is dissolved in 120 minutes.●5

B: To a solution (1 in 100) add an equal volume of alcohol: a translucent, gelatinous precipitate is formed (*distinction from most gums*).

C: ~~To 10 mL of a solution (1 in 100) add 1 mL of thorium nitrate TS, stir, and allow to stand for 2 minutes: a stable precipitate or gel forms (*distinction from gums*).~~

~~**D:**~~

■■1S *(USP29)*
To 5 mL of a solution (1 in 100) add 1 mL of 2 N sodium hydroxide, and allow to stand at room temperature for 15 minutes: a gel or semigel forms (*distinction from tragacanth*).

~~**E:**~~

■**D:**■1S *(USP29)*
Acidify the gel from the preceding test with 3 N hydrochloric acid, and shake: a voluminous, colorless, gelatinous precipitate forms, which upon boiling becomes white and flocculent (*pectic acid*).

BRIEFING

Phenylephrine Bitartrate, page 2028 of *PF* 30(6) [Nov.–Dec. 2004]. On the basis of comments received, it is proposed to revise the limit of individual unknown impurity in the table under *Procedure* in the test for *Chromatographic purity.* The chemical name of the drug substance has also been revised to include the stereochemistry of tartaric acid.

(PA2: D. Bempong) RTS—42389-1

BRIEFING

Pectin, *USP 28* page 1477. On the basis of comments received, it is proposed to delete *Identification* test *C* because of its use of a radioactive material, thorium nitrate.

(EMC: C. Sheehan) RTS—42430-1

Change to read:

Identification—

A: Heat 1 g with 9 mL of water on a steam bath until a solution is formed, replacing water lost by evaporation: it forms a stiff gel on cooling.

Add the following:

■Phenylephrine Bitartrate

Change to read:

$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.3

R-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol-, ~~hydrogen tartrate.~~■(2*R*,3*R*)-2,3-dihydroxybutanedioate (1 : 1) (salt).■1S *(USP29)*

(–)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogen tartrate.

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(–)-3 Hydroxy-α-[(methylamino)methyl] benzenemethanol, hydrogen tartrate.

1-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol, hydrogen tartrate [~~*17162-39-0*~~ ■*17162-39-9*■IS *(USP29)*].

» Phenylephrine Bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{13}NO_2 \cdot C_4H_6O_6$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Norphenylephrine Hydrochloride RS. USP Phenylephrine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The alkaline ~~of tartrate~~ filtrate from the test for *Specific rotation* responds positively to the test for *Tartrate* ⟨191⟩.

Specific rotation ⟨781S⟩**:** between –53° and –57° for the prepared sample.

Test solution—Prepare a sample solution of about ~~24~~ 240 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at 105° for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.

pH ⟨791⟩**:** between 3.0 and 4.0 in 10% w/v aqueous solution.

Loss on drying ⟨731⟩—Dry at 105° to a constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Change to read:

Chromatographic purity—

Buffer solution—Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (9 : 1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (9 : 1).

Diluent—Prepare a mixture of *Solution A* and *Solution B* (8 : 2).

System suitability solution—Dissolve accurately weighed quantities of USP Phenylephrine Hydrochloride RS~~, norphenylephrine hydrochloride, 1-benzylphenylepherine base, and benzylphenylepherine hydrochloride~~ and USP Norphenylephrine Hydrochloride RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about ~~0.06 mg per mL, 0.09 mg per mL, 0.07 mg per mL, and 0.05 mg per mL~~ 1.0 mg per mL and 0.9 µg per mL, respectively.

Blank solution—Prepare a solution containing 0.8 mg per mL L(+)-tartaric acid in *Diluent*.

Test solution—Transfer 78 mg of Phenylephrine Bitartrate, 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 215-nm detector and a 4-mm × 5.5-cm column that contains packing L1. The column temperature and injector temperature are maintained at 45 ± 2°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

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Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	93	7	equilibration
0–10	93→~~30~~ 70	7→~~70~~ 30	linear gradient
10–~~18~~ 10.1	~~30~~ 70→93	~~70~~-30→7	~~isocratic~~ linear gradient
10.1–18	93	7	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.9 for norphenylephrine, about 1.0 for (–)-phenylephrine, about 1.2 for phenylephrone, about 2.9 for 1-benzylphenylepherine, and about 3.1 for benzylphenylepherine HCl.~~ the resolution, *R,* between norphenylephrine and (–)-phenylephrine is not less than 1.5; the tailing factor of (–)-phenylephrine is less than 1.8; and the relative standard deviation for replicate injections is not more than ~~6%~~ 5%.

Procedure—~~Inject about 10 µL of~~ Separately inject equal volumes (about 4 µL) of the *Blank 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 Phenylephrine Bitartrate 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 0.5% of total impurities is found.~~ [NOTE—Examine the chromatogram of the *Blank solution* for peaks and disregard any corresponding peaks observed in the chromatogram of the *Test solution*.] The limits of impurities are specified in the accompanying table.

Compound	Approximate Relative Retention Time	Limit (%)
Phenylephrine	1.0	—
Norphenylephrine	0.9	0.2
Phenylephrone	1.2	0.1
Benzylphenylephrine	2.9	0.2
Benzylphenyl-ephrone	3.1	0.1
Individual unknown impurity	—	~~0.2~~ ■0.1■1S (*USP29*)
Total impurity	—	0.5

Assay—Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a 100-mL beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank determination (see *Titrimetry* ⟨541⟩), and make the necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 31.73 mg of $C_9H_{13}NO_2 \cdot C_4H_6O_6$.■2S (*USP28*)

In-Process Revision

BRIEFING

Potassium Bitartrate, *USP 28* page 1583; **Potassium Sodium Tartrate,** *USP 28* page 1599; **Sodium Bicarbonate,** *USP 28* page 1775. It is proposed to replace the odor perception method in the test for *Limit of ammonia* with a colorimetric test based on the iodophenol blue color reaction. A simple limit test is proposed for *Sodium Bicarbonate;* for *Potassium Bitartrate* and *Potassium Sodium Tartrate,* the proposed procedure includes a comparison to a color of the *Standard solution,* because an observable blue color may develop at a very low concentration of ammonia.

Because the limit of ammonia in the current test is not clear, the proposed limits reflect the quality of the materials available on the market. Interested parties are encouraged to submit comments to the Expert Committee.

(PA4: E. Gonikberg) RTS—42377-1

Change to read:

Limit of ammonia~~— Heat 500 mg of it with 5 mL of 1 N sodium hydroxide: no ammonia odor is detected.~~

■*Sodium hypochlorite solution*—Use a commercially available solution that contains between 4.0% and 6.0% of NaOCl.

Oxidizing solution—[NOTE—Prepare on the day of use.] Prepare a mixture of alkaline sodium citrate TS and *Sodium hypochlorite solution* (4 : 1).

Diluted sodium nitroferricyanide solution—Prepare a mixture of water and sodium nitroferricyanide TS (10 : 1).

Standard solution—Transfer 300 mg of ammonium chloride, previously dried over silica gel for 4 hours, to a 1-L volumetric flask, and dilute with water to volume. This solution contains 100 µg of ammonia per mL. Dilute this solution quantitatively and stepwise, if necessary, with water to obtain a solution having a concentration of 0.25 µg of ammonia per mL.

Test solution—Transfer 250 mg of Potassium Bitartrate to a 100-mL volumetric flask, dissolve in and dilute with water to volume. Heat gently to facilitate the dissolution.

Procedure—[NOTE—Carefully follow this order of addition.] Separately transfer 6.0 mL of each of the *Standard solution* and the *Test solution* to two color comparison tubes. To each tube, add 0.4 mL of phenol TS, 0.4 mL of *Diluted sodium nitroferricyanide solution,* 1.0 mL of *Oxidizing solution,* dilute with water to 10 mL, mix, and let stand for 1 hour: the color of the *Test solution* is not darker than the color of the *Standard solution* (0.01%).■1S (*USP29*)

BRIEFING

Potassium Iodide Oral Solution, *USP 28* page 1595. It is proposed to revise the *Note* in the Definition to indicate that those products that have been demonstrated to be stable for longer periods of time without the addition of thiosulfate are exempt from the thiosulfate requirement.

(PA7b: B. Davani) RTS—42302-1

Change to read:

» Potassium Iodide Oral Solution contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of KI.

NOTE—If Potassium Iodide Oral Solution is not to be used within a short time, add 0.5 mg of sodium thiosulfate for each g of KI.

■Products that have data to demonstrate acceptable stability without the addition of thiosulfate are exempt from this requirement.■1S (*USP29*)

Crystals of potassium iodide may form in Potassium Iodide Oral Solution under normal conditions of storage, especially if refrigerated.

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BRIEFING

Potassium Sodium Tartrate, *USP 28* page 1599—See briefing under *Potassium Bitartrate.*

(PA4: E. Gonikberg) RTS—42377-2

Change to read:

Limit of ammonia— ~~Heat a 5-mL portion of a solution (1 in 10) with 5 mL of 1 N sodium hydroxide: the odor of ammonia is not noticeable.~~

■*Sodium hypochlorite solution*—Use a commercially available solution that contains between 4.0% and 6.0% of NaOCl.

Oxidizing solution—[NOTE—Prepare on the day of use.] Prepare a mixture of alkaline sodium citrate TS and *Sodium hypochlorite solution* (4 : 1).

Diluted sodium nitroferricyanide solution—Prepare a mixture of water and sodium nitroferricyanide TS (10 : 1).

Standard solution—Transfer 300 mg of ammonium chloride, previously dried over silica gel for 4 hours, to a 1-L volumetric flask, and dilute with water to volume. This solution contains 100 µg of ammonia per mL. Dilute this solution quantitatively and stepwise, if necessary, with water to obtain a solution having a concentration of 1.0 µg of ammonia per mL.

Test solution—Transfer 5.0 g of Potassium Sodium Tartrate to a 100-mL volumetric flask, dissolve in and dilute with water to volume.

Procedure—[NOTE—Carefully follow this order of addition.] Separately transfer 4.0 mL of each of the *Standard solution* and the *Test solution* to two color comparison tubes. To each tube, add 0.4 mL of phenol TS, 0.4 mL of *Diluted sodium nitroferricyanide solution,* 1.0 mL of *Oxidizing solution,* dilute to 10 mL with water, mix, and let stand for 1 hour: the color of the *Test solution* is not darker than the color of the *Standard solution* (0.002%).■1S *(USP29)*

BRIEFING

Ramipril, *USP 28* page 1701 and page 2032 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to correct the concentration of the ion-pairing agent and the injection volume in the *Assay.*

(PA5: A.Wilk) RTS—40611-2

Change to read:

» Ramipril contains not less than 98.0 percent and not more than ~~101.0~~

■102.0■1S *(USP29)* percent of $C_{23}H_{32}N_2O_5$, calculated on the dried basis.

Change to read:

Assay— ~~Dissolve about 300 mg of Ramipril, accurately weighed, in 25 mL of methanol, add 25 mL of water, and titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N sodium hydroxide is equivalent to 41.65 mg of $C_{23}H_{32}N_2O_5$.~~

■*Sodium dodecyl sulfate solution*—Prepare a ~~1%~~ 0.1% solution of sodium dodecyl sulfate. Adjust with phosphoric acid to a pH of 2.4 ± 0.1, filter, and degas.

Mobile phase—Prepare a mixture of *Sodium dodecyl sulfate solution* and acetonitrile (55 : 45). Adjust with phosphoric acid to a pH of 2.75 ± 0.1, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve accurately weighed quantities of USP Ramipril RS and USP Ramipril Related Compound A RS in *Mobile phase* to obtain a solution having known concentrations of about 0.2 mg per mL and 0.01 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Ramipril RS in *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Transfer about 100 mg of Ramipril, accurately weighed, to a 100-mL volumetric flask, dissolve in about 10 mL of acetonitrile, dilute with *Mobile phase* to volume, and mix. Pipet about 10 mL of this stock 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 210-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.8 mL per minute. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ramipril and ramipril related compound A is not less than 2.0; the column efficiency determined from the ramipril peak is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections determined from the ramipril peak is not more than 1.0%.

Procedure—Separately inject equal volumes (about ~~10 µL~~ 20 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 $C_{23}H_{32}N_2O_5$ in the portion of Ramipril taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Ramipril 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 (*USP29*)

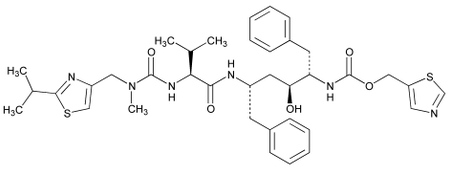
BRIEFING

Ritonavir. 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 procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the YMC Butyl C4 brand of L26 column (see *Chromatography* ⟨621⟩). The retention time for ritonavir is between 30 and 35 minutes.

(PA7b: B. Davani) RTS—41225-1

Add the following:

■Ritonavir



$C_{37}H_{48}N_6O_5S_2$ 720.94

2.4.7.12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolylmethyl ester [5*S*-(5*R**,8*R**,10*R**,11*R**)].

5-Thiazolylmethyl [(α*S*)-α-[1*S*,3*S*)-1-hydroxy-3-[(2*S*)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]carbamate [*155213-67-5*].

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» Ritonavir contains not less than 97.0 percent and not more than 102.0 percent of $C_{37}H_{48}N_6O_5S_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store between 5° and 30°.

USP Reference standards ⟨11⟩**—***USP Ritonavir RS. USP Ritonavir Related Compounds Mixture RS.*

Identification—

A: *Infrared Absorption* ⟨197S⟩—

Test specimen—Dissolve 50 mg of Ritonavir in 1.0 mL of chloroform. Add 1 drop of this solution to the surface of a potassium bromide or a sodium chloride disc, and evaporate to dryness.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* is within 2% of the retention time of the major peak in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

C: *X-Ray diffraction* ⟨941⟩—The X-ray diffraction pattern conforms to that of USP Ritonavir RS.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%, using 1.0 g of Ritonavir and 2 mL of *Standard Lead Solution* (10 ppm Pb) in the *Standard Preparation.*

Water, *Method I* ⟨921⟩**:** not more than 0.5%, determined on 0.500 g.

Residue on ignition ⟨281⟩**:** not more than 0.2%, determined on 1.0 g.

Organic volatile impurities ⟨467⟩**:** meets the requirements.

Related compounds—[NOTE—Ritonavir is alkaline sensitive. All glassware should be prerinsed with distilled water prior to use to remove residual detergent contamination.]

Monobasic potassium phosphate solution (0.03M)—Dissolve about 8.2 g of monobasic potassium phosphate in 2.0 L of water. Mix well, and filter through a 0.45-µm nylon membrane.

Diluent—Prepare a mixture of *Monobasic potassium phosphate solution (0.03M)* and acetonitrile (1 : 1). Mix well, and filter through a 0.45-µm nylon membrane.

Solution A—Prepare a mixture of the filtered *Monobasic potassium phosphate solution (0.03M)*, acetonitrile, tetrahydrofuran (inhibitor-free), and *n*-butanol (69 : 18 : 8 : 5).

Solution B—Prepare a mixture of the filtered *Monobasic potassium phosphate solution (0.03M)*, acetonitrile, tetrahydrofuran (inhibitor-free), and *n*-butanol (40 : 47 : 8 : 5).

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⟩). [NOTE—Because of the high dependence of retention time and selectivity on the *Mobile phase* composition, the volumes should be accurately measured. Excessive or continued helium sparging must be avoided. Store the *Mobile phase* in a tightly sealed container when not in use.]

Ritonavir identity standard solution—Transfer about 50 mg of USP Ritonavir Related Compounds Mixture RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Standard stock solution—Transfer about 100 mg of USP Ritonavir RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix. [NOTE—This solution may be kept for 5 days if refrigerated.]

Intermediate standard solution—Transfer 5.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard solution—Transfer 5.0 mL of the *Intermediate standard solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. [NOTE—This solution may be used for 48 hours if stored at room temperature.]

Test solution—Transfer about 50 mg of Ritonavir, 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 240-nm detector and a 4.6-mm × 15-cm column that contains 3-µm L26 packing and is maintained at a constant temperature of about 60°. 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	equilibrium
0–60	100	0	isocratic
60–120	100→0	0→100	gradient
120.1	0→100	100→0	step gradient
120.1–155	100	0	isocratic

The run time for the *Standard solution* is 40 minutes and the run time for the *Test solution* is 155 minutes. Chromatograph the *Ritonavir identity standard solution,* and the *Standard solution,* and record the responses as directed for *Procedure:* the retention time of ritonavir is between 30 and 35 minutes; the resolution, *R,* between impurity E and impurity F in the *Ritonavir identity standard solution* is not less than 1.0; the ratio of peak (H_p) to valley (H_v) of impurity N (regioisomer) is not less than 1; the capacity factor, *k′,* using the main component peak of the first *Standard solution* injection, is not less than 13; the column efficiency, using the main component peak of the first *Standard solution* injection, is not less than 5000 theoretical plates; the tailing factor, using the main component peak of the first *Standard solution* injection, is between 0.8 and 1.2; and the relative standard deviation of the peak area response of the main component peak, for replicate injections of the *Standard solution,* is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Diluent, Ritonavir identity standard solution, Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Ritonavir taken by the formula:

$$0.0025(W_S / W_T)\ (R_T / R_S)(1/F)P,$$

in which W_S is the the weight, in mg, of the USP Ritonavir RS taken to prepare the *Standard solution;* W_T is the weight, in mg, of Ritonavir taken to prepare the *Test solution;* R_T is the area of the impurity peak obtained from the *Test solution;* R_S is the average peak area of ritonavir obtained from the the six injections of *Standard solution; F* is the response factor for the impurity (see values in *Table 1);* and *P* is the purity, in percent, of the USP Ritonavir RS taken to prepare the *Standard solution.* Not more than 0.3% of impurity E and O is found; not more than 0.2% of impurity T is found; not more than 0.1% of any other impurity is found; and not more than 1.0% of total impurities is found.

Table 1. Approximate Relative Retention Time (RRT) for Known Related Impurities

Impurity Identity	Common Name	Response Factor	RRT
A + B	Mixture of 2,4-Wing acid and monoacyl valine	—	0.07
C	Monoacylacetamide	—	0.15
D	5-Wing diacyl	1.37	0.24
E	Oxidation impurity	—	0.36
F	Acid hydrolysis product	0.73	0.39
G	Ritonavir hydroperoxide	—	0.45
H	Acid/base by-product	0.76	0.47
I	Ethyl analog	—	0.64
J + K	Mixture of Boc-monoacyl and monoacyl isobutyl carbamate	0.74	0.81
L	Base cyclization product	0.53	0.87
M	2,4-Wing isobutyl ester	—	0.94
N	Regioisomer	—	1.05
O	Isomer #2	—	1.11
P	Di-monoacyl urea	—	1.14
Q	Isomer #4	—	1.23
R	Isomer #1	—	1.32
S	Di-monoacyl valine urea	—	1.62
T	2,4-Wing diacyl	0.73	2.87
U	Triacyl impurity	—	3.20

Assay—

Solution A, Solution B, Mobile phase, Diluent, and *Intermediate standard solution*—Proceed as directed in the test for *Related compounds.*

Standard preparation—Transfer 25.0 mL of the *Intermediate standard solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer 5.0 mL of the *Test solution,* prepared as directed in the test for *Related compounds,* to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Dilute 25.0 mL of this solution with *Diluent* to 100-mL, and mix.

Chromatographic system—Proceed as directed in the test for *Related compounds.*The run time for the *Standard preparation* and *Assay preparation* is 40 minutes. Chromatograph the *Standard preparation,*and record the responses as directed for *Procedure:* the capacity factor, k', using the main component peak of the first *Standard preparation* injection, is not less than 13; the column efficiency, using the main component peak of the first *Standard preparation* injection, is not less than 5000 theoretical plates; the tailing factor, using the main component peak of the first *Standard preparation* injection, is between 0.8 and 1.2; and the relative standard deviation of the peak area response of the main component peak, for replicate injections of the *Standard preparation,* 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 peak area responses. Calculate the percentage, on the as-is basis, of $C_{37}H_{48}N_6O_2S_2$ in the portion of Ritonavir taken by the formula:

$$0.5(W_S / W_T)(R_T / R_S)P,$$

in which W_S is the weight, in mg, of USP Ritonavir RS taken to prepare the *Standard preparation;* W_T is the weight, in mg, of Ritonavir taken to prepare the *Assay preparation;* R_T is the peak area of the impurity obtained from the chromatogram of the *Assay preparation;* R_S is the average peak area of ritonavir obtained from the chromatograms of the five injections of *Standard preparation;* and P is the purity, in percent, of the USP Ritonavir RS taken to prepare the *Standard preparation.*

Calculate the percentage, on the anhydrous basis, of $C_{37}H_{48}N_6O_2S_2$ in the portion of Ritonavir taken by the formula:

$$100A/(100 - B),$$

in which A is the percent of $C_{37}H_{48}N_6O_2S_2$ on the as-is basis, as calculated above, and B is the percent of water content.■1S (*USP29*)

BRIEFING

Simvastatin, *USP 28* page 1770 and page 1647 of *PF* 30(5) [Sept.–Oct. 2004]. It is proposed to replace the current methods for *Chromatographic purity, Limit of lovastatin,* and *Assay* with a single stability-indicating HPLC method. The separate test for *Limit of lovastatin* is being deleted; this test is now performed as a part of the test for *Chromatographic purity.* It is also proposed to replace the UV *Identification* test with the HPLC retention time agreement of the major peak in the chromatograms of the *Assay preparation* and the *Standard preparation.* The proposed methods are based on the analyses performed with the Perkin-Elmer Pecosphere C18 CR brand of L1 column; typical retention time of the simvastatin peak is about 2.5 minutes.

(PA4: E. Gonikberg) RTS—40244-1

Change to read:

Packaging and storage—Preserve in well-closed containers. ~~under nitrogen~~

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■Store between 15° and 30°, or under refrigeration.■2S *(USP28)*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197M⟩.
B: ~~*Ultraviolet Absorption* ⟨197U⟩~~
~~*Solution:* 10 µg per mL.~~
~~*Medium:* acetonitrile.~~

■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.*■1S *(USP29)*

Change to read:

Chromatographic purity—

~~*Diluting solution*—Prepare a solution of butylated hydroxytoluene in acetonitrile containing 0.5 mg per mL.~~

~~*Standard solutions*—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluting solution* to obtain *Standard solution A* having a known concentration of about 0.2 mg per mL. Transfer 4.0, 2.0, and 1.0 mL of *Standard solution A* to separate 10-mL volumetric flasks, and dilute with *Diluting solution* to volume to obtain *Standard solutions B*, *C*, and *D*, respectively.~~

~~*Test solution*—Dissolve an accurately weighed quantity of simvastatin in *Diluting solution* to obtain a solution having a concentration of about 20 mg per mL.~~

~~*Procedure*—Separately apply 4 µL portions of each of the *Standard solutions* and the *Test solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of silica gel mixture, previously washed with methanol and air-dried. Dry the spots with the aid of a stream of nitrogen. Position the plate in a chromatographic chamber previously equilibrated with a solvent system consisting of a mixture of cyclohexane, chloroform, and isopropyl alcohol (5 : 2 : 1) containing 0.5 mg of butylated hydroxytoluene per mL, and develop the chromatogram until the solvent front has moved about three-quarters of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate under a stream of nitrogen. Spray the plate with a mixture of methanol and sulfuric acid (8 : 2), heat at 110° for 30 minutes, and immediately examine the plate: no secondary spot in the chromatogram of the *Test solution* is greater in size or intensity than the principal spot from *Standard solution B* (0.4%), and the sum of all such secondary spots obtained from the *Test solution* is not greater than 1.0%.~~

■*Mobile phase, Diluent,* and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Inject about 5 µL of the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Simvastatin taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area for each impurity; and r_s is the sum of the areas of all the peaks. Not more than 1.0% of the sum of lovastatin and epilovastatin is found. [NOTE—If present, lovastatin and epilovastatin may not be completely resolved by the method. These peaks, appearing at a relative retention time of 0.6, should be integrated together to determine conformance.] Not more than 0.4% of any individual impurity other than lovastatin and epilovastatin is found; and not more than 1.0% of total impurities other than lovastatin and epilovastatin is found.■1S *(USP29)*

Delete the following:

■~~**Limit of lovastatin**—From the chromatograms of the *Assay preparation* and the *Standard preparation,* obtained as directed in the *Assay,* calculate the percentage of lovastatin in the portion of Simvastatin taken by the formula:~~

~~$$10{,}000(C / W)(r_u / r_s),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Lovastatin RS in the *Standard preparation; W* is the weight, in mg, of Simvastatin taken for the *Assay preparation;* and r_u and r_s are the lovastatin peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 1% is found.~~■1S *(USP29)*

Change to read:

Assay—

~~*Mobile phase*—Prepare a filtered and degassed mixture of acetonitrile and dilute phosphoric acid (1 in 1000) (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Diluting solution*—Prepare a mixture of acetonitrile and 0.01 M monobasic potassium phosphate (60 : 40), filter, and adjust with phosphoric acid to a pH of 4.0.~~

~~*Standard preparation*—Dissolve accurately weighed quantities of USP Simvastatin RS and USP Lovastatin RS in *Diluting solution*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.3 mg per mL of USP Simvastatin RS and 0.003 mg per mL of USP Lovastatin RS.~~

~~*Assay preparation*—Transfer about 30 mg of Simvastatin, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluting solution* to volume.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative retention times are about 0.65 for lovastatin and 1.0 for simvastatin, the resolution, *R*, between simvastatin and lovastatin is not less than 3.0, the column efficiency is not less than 2000~~

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~~theoretical plates, the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 1.0%.~~

~~*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 of the responses for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{38}O_5$ in the portion of Simvastatin taken by the formula:~~

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

~~in which *C* is the concentration, in mg per mL, of USP Simvastatin 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.~~

■*Solution A*—Prepare a mixture of acetonitrile and 0.1% phosphoric acid in water (1 : 1).

Solution B—Prepare a 0.1% solution of phosphoric acid in 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⟩).

Buffer solution—Prepare a solution containing 1.4 g of monobasic potassium phosphate per L, and adjust with phosphoric acid to a pH of 4.0.

Diluent—Prepare a mixture of acetonitrile and *Buffer solution* (3 : 2).

System suitability preparation—Dissolve accurately weighed quantities of USP Simvastatin RS and USP Lovastatin RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 1.5 mg per mL of USP Simvastatin RS and 0.015 mg per mL of USP Lovastatin RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluent* to obtain a solution having a known concentration of about 1.5 mg per mL.

Assay preparation—Transfer about 75 mg of Simvastatin, 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 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–4.5	100	0	isocratic
4.5–4.6	100→95	0→5	linear gradient
4.6–8.0	95→25	5→75	linear gradient
8.0–11.5	25	75	isocratic
11.5–11.6	25→100	75→0	linear gradient
11.6–13	100	0	re-equilibration

Chromatograph the *Standard preparation* and the *System suitability preparation,* and record the peak responses as directed for *Procedure*. For the *System suitability preparation,* the relative retention times are about 0.60 for lovastatin and 1.0 for simvastatin; and the resolution, *R,* between simvastatin and lovastatin is greater than 3. For the *Standard preparation,* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure

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the areas of the major peaks. Calculate the quantity, in mg, of $C_{25}H_{38}O_5$ in the portion of Simvastatin taken by the formula:

$$VC(r_U / r_S),$$

in which V is the volume, in mL, of the *Assay preparation;* C is the concentration, in mg per mL, of USP Simvastatin RS in the *Standard preparation;* and r_U and r_S are the responses of the simvastatin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

Oxidizing solution—[NOTE—Prepare on the day of use.] Prepare a mixture of alkaline sodium citrate TS and *Sodium hypochlorite solution* (4 : 1).

Diluted sodium nitroferricyanide solution—Prepare a mixture of water and sodium nitroferricyanide TS (10 : 1).

Test solution—Transfer 2.5 g of Sodium Bicarbonate to a 100-mL volumetric flask, dissolve in and dilute with water to volume.

Procedure—[NOTE—Carefully follow this order of addition.] To 4.0 mL of the *Test solution,* add 0.4 mL of phenol TS, 0.4 mL of *Diluted sodium nitroferricyanide solution,* 1.0 mL of *Oxidizing solution,* dilute with water to 10 mL, mix, and let stand for 1 hour: no blue color develops (0.002%).■1S (*USP29*)

BRIEFING

Sodium Bicarbonate, *USP 28* page 1775. The following changes are proposed:

1. *Limit of ammonia*—See briefing under *Potassium Bitartrate*.
2. *Normal carbonate*—Comments were received that a solubility problem was encountered when performing this test at a temperature not exceeding 5°. It is proposed to perform this test at a temperature not exceeding 15°, as was previously official in *USP VIII* through *USP XX*.

(PA4: E. Gonikberg) RTS—42377-3; 42380-1

Change to read:

Normal carbonate—Add 2.0 mL of 0.10 N hydrochloric acid and 2 drops of phenolphthalein TS to 1.0 g of Sodium Bicarbonate, previously dissolved without agitation in 20 mL of water at a temperature not exceeding ~~5°:~~

■15°:■1S (*USP29*)
the solution does not assume more than a faint pink color immediately.

Change to read:

Limit of ammonia~~— Heat about 1 g in a test tube: no odor of ammonia is evolved.~~

■*Sodium hypochlorite solution*—Use a commercially available solution that contains 4.0% to 6.0% of NaOCl.

BRIEFING

Sodium Chloride, *USP 28* page 1779. It is proposed to revise the *Identification* test, the test for *Loss on drying,* and the test for *Limit of potassium* to align the monograph with the harmonization text presented by the Pharmacopeial Discussion Group. In the *Identification* test references to USP General Chapters are omitted and replaced with tests *A, B, C,* and *D*. A tolerance of ± 10% is added to the sample weight under the test for *Loss on drying*. In addition, it is proposed to clarify the *Procedure* in the test for *Limit of potassium* to indicate that atomic emission spectrophotometry is used.

(PA1: J. Lane) RTS—42477-1

Change to read:

Identification~~— It responds to the tests for *Sodium* ⟨191⟩ and for *Chloride*.~~

■**A:** Dissolve in 2 mL of water a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl^-). Acidify with diluted nitric acid, and add 0.4 mL of a silver nitrate solution containing about 42.5 g per L. Shake,

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and allow to stand. A curdled, white precipitate is formed. Centrifuge, and wash the precipitate with three quantities, each 1 mL, of water. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in 2 mL of water, and add 1.5 mL of ammonium hydroxide. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

B: Introduce into a test tube a quantity of the substance to be examined equivalent to about 15 mg of chloride (Cl^-). Add 0.2 g of potassium dichromate and 1 mL of sulfuric acid. Place a filter-paper strip impregnated with 0.1 mL of *Diphenylcarbazide solution* over the opening of the test tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

Diphenylcarbazide solution—Dissolve 0.2 g of diphenylcarbazide in 10 mL of glacial acetic acid, and dilute with alcohol to 100 mL. Prepare immediately before use.

C: Dissolve 0.1 g of the substance to be examined in 2 mL of water. Add 2 mL of a 150 g per L solution of potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of *Potassium pyroantimonate solution,* and heat to boiling. Allow to cool in iced water, and if necessary rub the inside of the test tube with a glass rod. A dense white precipitate is formed.

Potassium pyroantimonate solution—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution containing 8.5 g of sodium hydroxide in 100 mL of water. Allow to stand for 24 hours, filter, and dilute with water to 150 mL.

D: Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na^+) in 0.5 mL of water. Add 1.5 mL of *Methoxyphenylacetic reagent,* and cool in ice water for 30 minutes. A voluminous, white, crystalline precipitate is formed. Place in water at 20°, and stir for 5 minutes. The precipitate does not disappear. Add 1 mL of ammonia TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution (158 g per L). No precipitate is formed.

Methoxyphenylacetic reagent—Dissolve 2.7 g of methoxyphenylacetic acid in 6 mL of 10% tetramethylammonium hydroxide solution in methanol, and add 20 mL of alcohol. Store in a polyethylene container.■1S (*USP29*)

Change to read:

Loss on drying ⟨731⟩—Dry the test material at 105° for 2 hours: it loses not more than 0.5% of its weight, determined on ~~a 1.000-g sample.~~

■about 1.000 g of sample.■1S (*USP29*)

Change to read:

Limit of potassium (where it is labeled as intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)—

Test solution—Transfer 1.00 g of Sodium Chloride to a 100-mL volumetric flask, add water and swirl to dissolve, dilute with water to volume, and mix.

Standard solution—[NOTE—The *Standard solution* and the *Test solution* may be modified, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument.] Dissolve 1.144 g of potassium chloride, previously dried at 105° for 3 hours, in water, dilute with water to 1000 mL, and mix. This solution contains the equivalent of 600 µg of potassium per mL. Dilute as required to obtain not fewer than three solutions at concentrations that span the expected value in the *Test solution*.

Procedure—Using atomic ~~absorption~~

■emission■1S (*USP29*) spectrophotometry (see *Spectrophotometry and Light-Scattering* ⟨851⟩), measure, at least three times, the emission intensity of the *Test solution* and the *Standard solution* using an air–acetylene flame and a wavelength of 766.5 nm. Prepare a calibration curve from the mean of the readings obtained with the *Standard solution,* and determine the concentration of potassium in the *Test solution.* The limit is 0.05%.

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BRIEFING

Sodium Citrate and Citric Acid Oral Solution, *USP 28* page 1783—See briefing under *Anticoagulant Sodium Citrate Solution.*

(PA5: A. Wilk; D. Bempong) RTS—42196-16

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.* ■1S (*USP29*)

(Official April 1, 2009)

Change to read:

Assay for sodium citrate—

~~*Cation-exchange column*—Mix 10 g of styrene-divinylbenzene cation-exchange resin with 50 mL of water in a suitable beaker. Allow the resin to settle, and decant the supernatant until a slurry of resin remains. Pour the slurry into a 15-mm × 30-cm glass chromatographic tube (having a sealed-in, coarse-porosity fritted disk and fitted with a stopcock), and allow to settle as a homogeneous bed. Wash the resin bed with about 100 mL of water, closing the stopcock when the water level is about 2 mm above the resin bed.~~

~~*Procedure*—Transfer an accurately measured volume of Oral Solution, equivalent to about 1 g of sodium citrate dihydrate, to a 100-mL volumetric flask; dilute with water to volume; and mix. Pipet 5 mL of this solution carefully onto the top of the resin bed in the *Cation-exchange column.* Place a 250-mL conical flask below the column, open the stopcock, and allow to flow until the solution has entered the resin bed. Elute the column with 60 mL of water at a flow rate of about 5 mL per minute, collecting about 65 mL of the eluate. Add 5 drops of phenolphthalein TS to the eluate, swirl the flask, and titrate with 0.02 N sodium hydroxide VS. Record the buret reading, and calculate the volume *(B)* of 0.02 N sodium hydroxide consumed. Calculate the quantity, in mg, of sodium citrate dihydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) in each mL of the Oral Solution taken by the formula:~~

$$[1.961B(20/V)] - [(294.10/210.14)C],$$

~~in which 1.961 is the equivalent, in mg, of $C_6H_5Na_3O_7 \cdot 2H_2O$, of each mL of 0.02 N sodium hydroxide; *V* is the volume, in mL, of Oral Solution taken; 294.10 and 210.14 are the molecular weights of sodium citrate dihydrate and citric acid monohydrate, respectively; and *C* is the concentration, in mg per mL, of citric acid monohydrate in the Oral Suspension, as obtained in the *Assay for citric acid.*~~

■*Mobile Phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of Oral Solution, equivalent to about 1 g of sodium citrate dihydrate, into a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under general chapter ⟨345⟩

Procedure—Proceed as directed for *Procedure* under general chapter ⟨345⟩, and calculate the quantity, in mg per mL, of sodium citrate dihydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$) in the Oral Solution taken by the formula:

$$0.001C(294.10/189.10)(D/V)(r_U/r_S) - (294.10/210.14)A,$$

in which C is the concentration, in µg per mL, of citrate in *Standard Preparation 1;* 294.10, 189.10, and 210.14 are the molecular weights of sodium citrate dihydrate ($C_6H_5Na_3O_7 \cdot 2H_2O$), citrate ($C_6H_5O_7$), and citric acid monohydrate ($C_6H_8O_7 \cdot H_2O$), respectively; D is the dilution factor; V is the volume of Oral Solution used to prepare the *Assay preparation;* r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard preparation 1,* respectively; and A is the concentration of citric acid monohydrate, in mg per mL, determined in the *Assay for citric acid.* ■1S (*USP29*)

(Official April 1, 2009)

BRIEFING

Sulfamethazine Granulated, *USP 28* page 1826. For further clarification of the procedure in the *Assay,* it is proposed to add the particle size of the HPLC analytical column specified for the

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Chromatographic system. In addition, minor editorial style changes have been made. Interested parties are encouraged to submit comments to the USP Veterinary Drugs Expert Committee.

(VET: I. DeVeau) RTS—42381-1

Change to read:

Assay—

Mobile phase—Prepare a mixture of water, methanol, and glacial acetic acid (68 : 30 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Extractant—Prepare a mixture of 0.15 N hydrochloric acid and methanol (3 : 1).

Standard preparation—Prepare a solution of USP Sulfamethazine RS in *Extractant* having a known concentration of about 0.01 mg per mL.

Assay preparation—Transfer about 5 g of Sulfamethazine Granulated, accurately weighed, to a suitable container, add 250.0 mL of *Extractant*, and shake by mechanical means for 2 hours. Allow the mixture to settle, storing the mixture in a refrigerator if settling is allowed to continue overnight. Filter a portion of the supernatant, and transfer 10.0 mL of the clear filtrate to a 100-mL volumetric flask. Dilute with *Extractant* to volume, and mix. Transfer 5.0 mL of this solution to a 200-mL volumetric flask, dilute with *Extractant* to volume, and mix. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Assay preparation*. This solution contains about 0.01 mg of sulfamethazine per mL.

Derivatizing reagent—Dissolve 6.0 g of dimethylaminobenzaldehyde in 200 mL of glacial acetic acid, add 120 mL of methanol and 80 mL of water, mix, and degas. Prepare this reagent daily.

Chromatographic system—The liquid chromatograph is equipped with a guard column that contains packing L1, a 4.6-mm × 25-cm analytical column that contains

■10-µm■1S *(USP29)*
packing L1, a separate pump to deliver the *Derivatizing reagent* via a T-junction installed immediately postcolumn, a postcolumn derivatization coil consisting of 3-m × 0.5-mm inside-diameter polytef tubing, a flow cell, and a 450-nm detector. The *Mobile phase* flow rate is about 2 mL per minute, and the *Derivatizing reagent* 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', for the sulfamethazine peak is not less than 2.0; and the relative standard deviation for replicate injections is not more than 3.5%.

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 sulfamethazine peaks. Calculate the quantity, in mg, of sulfamethazine ($C_{12}H_{14}N_4O_2S$) in each g of the Sulfamethazine Granulated taken by the formula:

$$100{,}000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Sulfamethazine RS in the *Standard preparation, W* is the quantity, in g, of Sulfamethazine Granulated taken to prepare the *Assay preparation,* and r_U and r_S are the sulfamethazine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Thioridazine Hydrochloride, *USP 28* page 1916. It is proposed to revise *Identification* test *B* to increase the solubility of the free base by modifing the solution with a suitable solvent.

(PA3: R. Ravichandran) RTS—42334-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: ~~A solution (1 in 10) responds to the tests for *Chloride* ⟨191⟩.~~

■A solution (1 in 100) in a mixture of water and alcohol (1 : 1) responds to the test for *Chloride* ⟨191⟩ in amine hydrochlorides.■1S *(USP29)*

BRIEFING

Tilmicosin, *USP 28* page 1931. It is proposed to clarify the Definition regarding the content of tilmicosin *trans*-isomers, to revise the test for *Related compounds* to change the relative retention times in the *Chromatographic system* and clarify the designated potency of tilmicosin in the *Procedure*, and to revise the *Assay* to add a *Note* under *Chromatographic system*. Interested parties are encouraged to submit comments to the Expert Committee on Veterinary Drugs.

(VET: I. DeVeau) RTS—42339-1

Change to read:

» Tilmicosin contains not less than 85.0 percent of $C_{46}H_{80}N_2O_{13}$, calculated on the anhydrous basis. The content of tilmicosin *cis*-isomers is between 82.0 percent and 88.0 percent, and the content of tilmicosin *trans*-isomers is between 12.0 percent and 18.0 percent

■of total $C_{46}H_{80}N_2O_{13}$.■1S *(USP29)*

Caution—Tilmicosin is irritating to the eyes and may cause allergic reaction. Avoid contact.

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Change to read:

Related compounds—

Dibutylammonium phosphate buffer and *Diluent*—Prepare as directed in the *Assay.*

Solution A—To 700 mL of water add 25 mL of *Dibutylammonium phosphate buffer*, dilute with water to volume, and mix. Degas before use.

Solution B—Use 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—Dissolve an accurately weighed quantity of USP Tilmicosin RS in acetonitrile to obtain a solution having a known concentration of about 0.25 mg per mL, sonicating if necessary to dissolve. Transfer 5.0 mL of this solution to a 25-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 200 mg of Tilmicosin, accurately weighed, to a 50-mL volumetric flask, add 10 mL of acetonitrile, and sonicate briefly to dissolve. Dilute with *Diluent* to volume, and mix. [NOTE—Use this solution within 24 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1 and is programmed for gradient elution by delivering a mixture of *Solution A* and *Solution B* in a ratio of 82 : 18 initially, and by continuously varying the mixture linearly over a period of 30 minutes until the final ratio is 60 : 40. The flow rate is about 1.1 mL per minute. Chromatograph the *Standard solution,* and record the responses as directed for *Procedure:* the relative retention times are about ~~0.8~~

■0.9■1S *(USP29)*
for the tilmicosin *trans*-isomers (two incompletely resolved peaks), ~~0.9~~

■1.0■1S *(USP29)*
for the tilmicosin *cis*-isomer, and ~~1.0~~

■1.1■1S *(USP29)*
for the tilmicosin *cis*-8-epimer.

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 area responses for the major peaks. Calculate the percentage of each related compound in the portion of Tilmicosin taken by the formula:

$$5(CP / W)(r_c / r_s),$$

in which C is the concentration, in mg per mL, of USP Tilmicosin RS in the *Standard solution; P* is the designated potency, in µg per mg, ~~of tilmicosin *trans*-isomers, tilmicosin *cis*-isomer, and tilmicosin *cis*-8-epimer, respectively. In the USP Tilmicosin RS~~

■of tilmicosin in the USP Tilmicosin RS;■1S *(USP29)*
W is the weight, in mg, of Tilmicosin taken to prepare the *Test solution;* r_c is the area response of the individual related compound peak, other than those obtained for tilmicosin *trans*-isomers, tilmicosin *cis*-isomer, and tilmicosin *cis*-8-epimer; and r_s is the sum of the peak area responses for the tilmicosin *trans*-isomers, the tilmicosin *cis*-isomer, and the tilmicosin *cis*-8-epimer obtained from the *Standard solution*. Not more than 3% of any individual related compound, calculated on the anhydrous basis, is found, and the sum of all the related compounds is not more than 10%, calculated on the anhydrous basis.

Change to read:

Assay—

Dibutylammonium phosphate buffer—Add, with stirring, 70 mL of dilute phosphoric acid (1 in 10) to 16.8 mL of dibutylamine (90 : 10). Allow to cool, and adjust with phosphoric acid to a pH of 2.5 ± 0.1. Dilute with water to 100 mL, and mix.

Mobile phase—To 700 mL of water, add 115 mL of acetonitrile, 55 mL of tetrahydrofuran, and 25 mL of *Dibutylammonium phosphate buffer.* Dilute with water to 1000 mL, and mix. Each component may be degassed before use, or the *Mobile phase* may be sparged with helium for 2 minutes before use. Store the *Mobile phase* in a sealed container when not in use. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Decreasing the proportion of acetonitrile or tetrahydrofuran increases resolution.]

Diluent—To 900 mL of water, add 5.71 g of phosphoric acid, adjust with 12.5 N sodium hydroxide to a pH of 2.5 ± 0.1, dilute with water to 1000 mL, and mix.

Standard preparation—Transfer about 25 mg of USP Tilmicosin RS, accurately weighed, to a 50-mL volumetric flask, add 10 mL of acetonitrile, and sonicate to dissolve. Dilute with *Diluent* to volume, and mix. [NOTE—Use this solution on the day prepared.]

Assay preparation—Transfer about 25 mg of Tilmicosin, accurately weighed, to a 50-mL volumetric flask, add 10 mL of acetonitrile, and sonicate to dissolve. Dilute with *Diluent* to volume, and mix. [NOTE—Use this solution on the day prepared.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-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 responses as directed for *Procedure:* the relative retention times are about 0.8 for the tilmicosin *trans*-isomers and 1.0 for the tilmicosin *cis*-isomers

■[NOTE—Tilmicosin *cis*-isomer and tilmicosin *cis*-8-epimer co-elute in this chromatographic system];■1S *(USP29)*
the resolution, R, between the tilmicosin *trans*-isomers peak and the tilmicosin *cis*-isomers peak is not less than 1.25; the tailing factors for the peaks are not less than 0.7 and 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 preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in µg, of tilmicosin *trans*- and *cis*-isomers in the portion of Tilmicosin taken by the formula:

$$50(CP / W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Tilmicosin RS in the *Standard preparation; P* is the designated potency, in µg per mg, of the relevant (*trans* or *cis*) tilmicosin isomers in the USP Tilmicosin RS; W is the weight, in mg, of Tilmicosin taken to prepare the *Assay preparation;* r_i is the peak area response for the relevant (*trans* or *cis*) tilmicosin isomers obtained from the *Assay preparation;* and r_S is the peak area response for the relevant (*trans* or *cis*) tilmicosin isomers obtained from the *Standard preparation*. Calculate the percentage of tilmicosin ($C_{46}H_{80}N_2O_{13}$) in the portion of Tilmicosin taken by the formula:

$$0.1(trans + cis),$$

in which *trans* and *cis* are the quantities, in µg per mg, of tilmicosin *trans*-isomers and tilmicosin *cis*-isomers in the Tilmicosin, as de-

termined above. Calculate the percentages of tilmicosin *trans*-isomers and tilmicosin *cis*-isomers taken by the formula:

$$100\ isomer / (trans + cis),$$

in which *isomer* is the quantity, in µg per mg, of either the tilmicosin *trans*-isomers or the tilmicosin *cis*-isomers in the Tilmicosin, as determined above.

BRIEFING

Triamcinolone Acetonide, *USP 28* page 1959 and page 3279 of the *First Supplement.* It is proposed to include the use of a USP Reference Standard, USP Fluoxymesterone RS, to replace fluoxymesterone in the *Internal standard solution* of the *Assay.*

(PA1: C. Anthony) RTS—42460-01

Change to read:

USP Reference standards ⟨11⟩—

■*USP Fluoxymesterone RS.*■1S *(USP29)*
USP Triamcinolone Acetonide RS.

Change to read:

Assay—

Mobile phase—Prepare a solution of acetonitrile in water containing approximately 30% (v/v) of acetonitrile.

Internal standard solution—Dissolve ~~fluoxymesterone~~

■USP Fluoxymesterone RS■1S *(USP29)* in methanol to obtain a solution having a concentration of about 50 µg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Triamcinolone Acetonide RS in *Internal standard solution* to obtain a solution having a known concentration of about 75 µg per mL. Mix an accurately measured volume of the resulting solution with an equal volume of *Mobile phase* to obtain a *Standard preparation* containing about 37.5 µg of USP Triamcinolone Acetonide RS per mL.

Assay preparation—Using about 37 mg of Triamcinolone Acetonide, accurately weighed, proceed as directed for *Standard preparation.*

Procedure—Introduce equal volumes (between 15 µL and 25 µL) of the *Assay preparation* and the *Standard preparation* into a high-pressure liquid chromatograph (see *Chromatography* ⟨621⟩) operated at room temperature, by means of a suitable microsyringe or sampling valve. Adjust the operating parameters with *Mobile phase* on the column so that the separation of triamcinolone acetonide and internal standard is optimized, with a retention time of about 14.5 minutes for triamcinolone acetonide. Typically, the apparatus is fitted with a 4-mm × 30-cm column containing packing L1 and is equipped with a UV detector capable of monitoring absorbance at 254 nm, and a suitable recorder. In a suitable chromatogram, the coefficient of variation for five replicate injections of a single specimen is not more than 3.0%; and the resolution factor, *R* (see *Chromatography* ⟨621⟩), between the peaks for triamcinolone acetonide and fluoxymesterone is not less than 2.0. Measure the heights of the internal standard and triamcinolone acetonide peaks at the same retention times obtained from the *Assay preparation* and the *Standard preparation.* Calculate the quantity, in mg, of $C_{24}H_{31}FO_6$ in the portion of Triamcinolone Acetonide taken by the formula:

$$1000C(R_U / R_S),$$

in which *C* is the concentration, in mg per mL, of USP Triamcinolone Acetonide RS in the *Standard preparation;* and R_U and R_S are the ratios of the peak heights of triamcinolone acetonide to the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ursodiol Capsules, *USP 28* page 2006 and page 79 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to correct the molar concentration of the *Medium* in the test for *Dissolution*.

(BPC: M. Marques) RTS—42318-1

Change to read:

Dissolution ⟨711⟩—

Medium: ~~0.2 M~~
★~~0.5 M~~★*USP29*

■0.05 M■1S *(USP29)* 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 ($C_{24}H_{40}O_4$) 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 *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.

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 and detector temperatures are maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as

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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.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{40}O_4$ is dissolved in 30 minutes.

BRIEFING

Valproic Acid Injection. The proposed new monograph for *Valproic Acid Injection*, previously published on page 940 of PF 26(4) [July–Aug. 2000], is hereby cancelled and replaced with the following new proposal. The *Assay* employs a gas chromatographic method using a 2-mm × 1.8-m glass column packed with 10% phase G34 on 80- to 100-mesh support S1A with biphenyl as the internal standard. Typical retention time for valproic acid is about 3 minutes, and that for biphenyl is about 7 minutes.

(PA3: R. Ravichandran; NL: L. Paul; AMB: R. Tirumalai; PSD: C. Okeke) RTS—22708-1; 22708-2; 22708-3; 22708-4

Add the following:

■Valproic Acid Injection

» Valproic Acid Injection is a sterile aqueous solution of sodium valproate, formed from the interaction of Valproic Acid and Sodium Hydroxide, in Water for Injection, and one or more suitable buffering or sequestering agents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of valproic acid ($C_8H_{16}O_2$). Valproic Acid Injection contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose *Containers for Injection* as described under *Injections* ⟨1⟩, preferably Type I glass. Store at controlled room temperature, 20° to 25°, excursions allowed between 15° and 30°.

Labeling—Label it to state the name and quantity of any buffering or sequestering agent used.

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Valproic Acid RS.*

Identification—

A: 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.*

B: It meets the requirements of the tests for *Sodium* ⟨191⟩.

Bacterial endotoxins ⟨85⟩**—**It contains not more than 23 USP Endotoxin Units per mL of Injection.

Sterility ⟨71⟩**—**It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product To Be Examined.*

pH ⟨791⟩**:** between 7.0 and 9.0.

Particulate matter ⟨788⟩**—**It meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Internal standard solution—Dissolve a quantity of biphenyl in methylene chloride to obtain a solution containing 5 mg per mL.

Standard stock preparation—Prepare a solution of USP Valproic Acid RS in *Internal standard solution* having a concentration of about 8 mg per mL.

Standard preparation—Transfer 5.0 mL of *Standard stock preparation* into a 50-mL volumetric flask, and dilute with methylene chloride to volume.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to 400 mg of sodium valproate, into a suitable container; add about 20 mL of 5% (v/v) hydrochloric acid; shake by mechanical means for 2 minutes; add 50.0 mL of *Internal standard solution;* and shake by mechanical means for 1 hour. Allow the phase to separate (approximately 1 hour). The bottom organic layer remains cloudy, and at times a slight emulsion may persist. The emulsion is easily broken up with the aid of a glass rod. Pipet 5 mL of the extract from the bottom organic layer into a 50-mL volumetric flask, and dilute with methylene chloride.

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 G34 on 80- to 100-mesh support S1A. The column temperature is maintained at about 155°, the injection port temperature is maintained at about 275°, and the detector block temperature is maintained at about 300°. Dry helium is used as the carrier gas at a flow rate of about 20 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the resolution, *R,* between the valproic acid and biphenyl peaks is not less than 3.0; and the relative standard deviation of the peak area ratios for replicate injections is not more than 2.0%.

Procedure—Separately inject equal amounts (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for the valproic acid and biphenyl peaks. Calculate the quantity, in mg, of valproic acid in the portion of Injection taken by the formula:

$$C(R_U / R_S)\, D,$$

in which C is the concentration, in mg per mL, of USP Valproic Acid RS in the *Standard preparation;* R_U and R_S are the peak area ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively; and D is the appropriate dilution factor used to prepare the *Assay preparation.* ■1S (*USP29*)

BRIEFING

Sterile Water for Inhalation, *USP 28* page 2034 and page 3282 of the *First Supplement*—See briefing under *Sterile Purified Water.*

(PW: F. Barletta) RTS—42231-2

Delete the following:

■**pH** ~~⟨791⟩: between 4.5 and 7.5, in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.~~ ■1S (*USP29*)

Delete 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 L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.~~ ■1S (*USP29*)

Delete the following:

■**Calcium**—~~To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.~~ ■1S (*USP29*)

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Delete the following:

■~~**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.~~■1S (*USP29*)

Delete 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 L), viewed downward over a dark surface with light entering the tubes from the sides.~~■1S (*USP29*)

Delete the following:

■~~**Sulfate**—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.~~■1S (*USP29*)

Add the following:

■**Conductivity** ⟨644⟩: not more than 25 µS/cm for containers 10 mL or less; not more than 5 µS/cm for containers greater than 10 mL at 25 ± 1°.■1S (*USP29*)

Change to read:

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~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of ~~0.1 N~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

BRIEFING

Sterile Water for Injection, *USP 28* page 2034 and page 3282 of the *First Supplement*—See briefing under *Sterile Purified Water*.

(PW: F. Barletta) RTS—42231-3

Delete 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 (*USP29*)

Delete 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 L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.~~■1S (*USP29*)

Delete the following:

■~~**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.~~■1S (*USP29*)

Delete the following:

■~~**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.~~■1S (*USP29*)

Delete 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 L), viewed downward over a dark surface with light entering the tubes from the sides.~~■1S (*USP29*)

Delete the following:

■~~**Sulfate**—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.~~■1S (*USP29*)

Add the following:

■**Conductivity** ⟨644⟩: not more than 25 µS/cm for containers 10 mL or less; not more than 5 µS/cm for containers greater than 10 mL at 25 ± 1°.■1S (*USP29*)

Change to read:

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~~

■0.02 N■1S (*USP29*)

potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of ~~0.1 N~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

BRIEFING

Sterile Water for Irrigation, *USP 28* page 2035—See briefing under *Sterile Purified Water.*

(PW: F. Barletta) RTS—42231-4

Delete 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 (*USP29*)

Delete 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 L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.~~■1S (*USP29*)

Delete the following:

■~~**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.~~■1S (*USP29*)

Delete the following:

■~~**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.~~■1S (*USP29*)

Delete 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 L), viewed downward over a dark surface with light entering the tubes from the sides.~~■1S (*USP29*)

Delete the following:

■~~**Sulfate**—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.~~■1S (*USP29*)

Add the following:

■**Conductivity** ⟨644⟩: not more than 25 µS/cm for containers 10 mL or less; not more than 5 µS/cm for containers greater than 10 mL at $25 \pm 1^{\circ}$.■1S (*USP29*)

Change to read:

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~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of ~~0.1 N~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

BRIEFING

Sterile Purified Water, *USP 28* page 2035 and page 3282 of the *First Supplement;* **Sterile Water for Irrigation,** *USP 28* page 2035. The Pharmaceutical Waters Expert Committee has previously proposed revisions of the packaged water monographs, but without success. Total organic carbon (TOC) testing primarily identifies the extractables from the container, and it is difficult to arrive at an acceptable limit. Conductivity testing, however, can be applied and in so doing several outmoded subjective "wet chemistry" tests can be deleted from the monographs. Therefore, the Committee proposes a conductivity test with limits that harmonize with the *European Pharmacopoeia.* Also, it is proposed to delete the *pH* standard because a sample cannot pass the test for *Conductivity* and fail the test for *pH;* i.e., the two tests are interrelated. The Committee retains the test for *Oxidizable substances* with a reduction in the potassium permanganate solution concentration, again to harmonize with the procedure described in the *European Pharmacopoeia.* However, the Committee continues to seek a replacement for the test for *Oxidizable substances* since it has been shown to produce questionable results. A new general chapter *Conductivity*

⟨644⟩, developed to provide the testing protocol, is found in this issue of *PF*. Comments should be addressed to Frank Barletta, Liaison to the Pharmaceutical Waters Expert Committee.

(PW: F. Barletta) RTS—42231-1

Delete 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 (*USP29*)

Delete 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 adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL)■1S (*USP29*) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.~~■1S (*USP29*)

Delete the following:

■**Calcium**— ~~To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.~~■1S (*USP29*)

Delete the following:

■**Carbon dioxide**— ~~To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.~~■1S (*USP29*)

Delete 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 ■a solution of sodium chloride in■1S (*USP29*) *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩), containing ■825 µg of sodium chloride per L (10 µg of Cl in 20 mL),■1S (*USP29*) viewed downward over a dark surface with light entering the tubes from the sides.~~■1S (*USP29*)

Delete the following:

■**Sulfate**— ~~To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.~~■1S (*USP29*)

Add the following:

■**Conductivity** ⟨644⟩: not more than 25 µS/cm for containers 10 mL or less; not more than 5 µS/cm for containers greater than 10 mL at $25 \pm 1°$.■1S (*USP29*)

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Purified Water in containers having a fill volume of less than 50 mL, add 0.4 mL of ~~0.1 N~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of ~~0.1 N~~

■0.02 N■1S (*USP29*)
potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 23* page 2941, page 3349 of the *First Supplement,* and page 2062 of *PF* 30(6) [Nov.–Dec. 2005]. It is proposed to add *Gamma Cyclodextrin* to the *Sequestering Agent* category. The proposed revision complements the proposed new monograph, *Gamma Cyclodextrin,* which appears elsewhere in this number of *PF.*

(EMC) RTS—41451-1

Add the following:

■In the following reference table, the grouping of excipients by functional category is intended to summarize the most typically identified purpose that these excipients serve in drug product formulations. The list of substances included in each category is not comprehensive. The statement of category is intended neither to limit in any way the choice or use of the substance nor to indicate that it has no other utility.■2S (*NF23*)

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Change to read:

Antifoaming Agent
Dimethicone

■Myristic Acid■2S (*NF23*)
■Palmitic Acid■1S (*NF23*)
Simethicone

Change to read:

Buffering Agent
Acetic Acid
▲Adipic Acid▲*NF23*
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
▲Citric Acid, Anhydrous▲*NF23*
▲Citric Acid Monohydrate▲*NF23*
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate

■Potassium Phosphate, Dibasic■2S (*NF23*)
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
▲Succinic Acid▲*NF23*

Change to read:

Coating Agent
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
▲Cellaburate▲*NF23*
Cellulose Acetate Phthalate (see Cellacefate)
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■2S (*NF23*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)

■Hypromellose Acetate Succinate■2S (*NF23*)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)

■Maltodextrin■2S (*NF23*)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
■Starch, Pregelatinized Modified■1S (*NF23*)
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Color
Caramel
Ferric Oxide, red, yellow, ~~black,~~

■■2S (*NF23*)
or blends

Change to read:

Emollient
Alkyl (C12-15) Benzoate
Hydrogenated Soybean Oil

■Polydecene■2S (*NF23*)

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Diglycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate

■Sorbitan Sesquioleate■2S (*NF23*)

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■Sorbitan Trioleate■2S (*NF23*)
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Flavors and Perfumes

■Almond Oil■2S (*NF23*)
Anethole
Benzaldehyde

■Ethyl Acetate■2S (*NF23*)
Ethyl Vanillin
■Maltol■1S (*NF23*)
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

Change to read:

Humectant

■Corn Syrup Solids■2S (*NF23*)
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol

■Sorbitol, Sorbitan Solution■2S (*NF23*)

■Tagatose■2S (*NF23*)

Change to read:

Ointment Base
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Diethylene Glycol Monoethyl Ether

■Lauroyl Macrogolglycerides■2S (*NF23*)
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Lanolin
Ointment, Hydrophilic
Ointment, White
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Ointment, Yellow
Polyethylene Glycol ~~Ointment~~

■Monomethyl Ether■2S (*NF23*)
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White

■Polydecene■2S (*NF23*)
Rose Water
Squalane

■Stearoyl Polyoxylglycerides■1S (*NF23*)
Vegetable Oil, Hydrogenated, Type II

Change to read:

Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol

■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol

■Sorbitol, Sorbitan Solution■2S (*NF23*)
Triacetin
Tributyl Citrate
Triethyl Citrate

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■1S (*NF24*)
▲Sodium Tartrate▲*NF23*

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

■Lauroyl Macrogolglycerides■2S (*NF23*)
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Peanut Oil

■Polydecene■2S (*NF23*)
Polyethylene Glycol

■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol
Sesame Oil

■Stearoyl Polyoxylglycerides■1S (*NF23*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar

■Alamic Acid■2S (*NF23*)
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 Copolymer

■Carbomer Homopolymer■2S (*NF23*)
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■2S (*NF23*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate

■Maltodextrin■2S (*NF23*)
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Tapioca
■Starch, Wheat■1S (*NF23*)
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
▲Acesulfame Potassium▲*NF23*
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■2S (*NF23*)
Dextrates
Dextrose
Dextrose Excipient
Fructose
▲Galactose▲*NF23*
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

■Tagatose■2S (*NF23*)

Change to read:

Tablet Binder
Acacia
Alginic Acid
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion

■Carbomer Homopolymer■2S (*NF23*)
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■2S (*NF23*)
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum

■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)

■Hypromellose Acetate Succinate■2S (*NF23*)

■Maltodextrin■2S (*NF23*)
Maltose
Methylcellulose
Polyethylene Oxide
Povidone
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Syrup

In-Process Revision

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■2S (*NF23*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose Monohydrate

■Maltodextrin■2S (*NF23*)
Maltose
Mannitol
Sorbitol
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Maltose
Polacrilin Potassium
Sodium Starch Glycolate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*

Change to read:

Tablet and/or Capsule Lubricant
Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light
Polyethylene Glycol

■Polyoxyl 10 Oleyl Ether■2S (*NF23*)

■Polyoxyl 20 Cetostearyl Ether■2S (*NF23*)

■Polyoxyl 35 Castor Oil■2S (*NF23*)

■Polyoxyl 40 Hydrogenated Castor Oil■2S (*NF23*)

■Polysorbate 20■2S (*NF23*)

■Polysorbate 40■2S (*NF23*)

■Polysorbate 60■2S (*NF23*)

■Polysorbate 80■2S (*NF23*)

■Sodium Lauryl Sulfate■2S (*NF23*)
Sodium Stearyl Fumarate

■Sorbitan Monolaurate■2S (*NF23*)

■Sorbitan Monooleate■2S (*NF23*)

■Sorbitan Monopalmitate■2S (*NF23*)

■Sorbitan Monostearate■2S (*NF23*)

■Sorbitan Sesquioleate■2S (*NF23*)

■Sorbitan Trioleate■2S (*NF23*)
Stearic Acid
Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

Change to read:

Tonicity Agent

■Corn Syrup Solids■2S (*NF23*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■2S (*NF23*)

■Dextrose■2S (*NF23*)
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

■Polydecene■2S (*NF23*)
Safflower Oil
Sesame Oil
Soybean Oil
Squalane

SOLID CARRIER
Sugar Spheres

STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

Change to read:

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride
Docusate Sodium
Nonoxynol 9
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate

■Sorbitan Sesquioleate■2S (*NF23*)

■Sorbitan Trioleate■2S (*NF23*)
Tyloxapol

In-Process Revision

MONOGRAPHS (NF)

BRIEFING

Acesulfame Potassium, *NF 23* page 2947 and page 87 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to revise the test for *Limit of fluoride* so that it corresponds to the procedure under *Acesulfame Potassium* in the *European Pharmacopoeia 5th Edition.*

(EMC: K. Russo) RTS—42330-1

Add the following:

▲**Packaging and storage—**Preserve in a well-closed container, and protect from light. Store at room temperature.▲*NF24*

Change to read:

Limit of fluoride—[NOTE—Use plasticware throughout this test.]

Buffer solution—Dissolve 210 g of citric acid monohydrate in 400 mL of water. Adjust with concentrated ammonia to a pH of 7.0, dilute with water to 1000 mL, and mix *(Solution A).* Dissolve 132 g of ~~monobasic~~

■dibasic■1S *(NF24)*
ammonium phosphate in water, dilute with water to 1000 mL, and mix *(Solution B).* To a suspension of 292 g of ~~edetate disodium~~

■edetic acid■1S *(NF24)*
in about 500 mL of water, add about 200 mL of ammonium hydroxide, and mix to dissolve *(Solution C).* Adjust with ammonium hydroxide to a pH between 6 and 7, dilute with water to make 1000 mL, and mix. Mix equal volumes of *Solution A, Solution B,* and *Solution C,* and adjust with ammonium hydroxide to a pH of 7.5.

Standard stock solution—Weigh accurately about 0.442 g of sodium fluoride, previously dried at 300° for 12 hours, into a 1-L volumetric flask, dilute with water to volume, and mix. Store the solution in a closed plastic container. Immediately before use, pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Each mL of this solution contains 10 µg of fluoride ion.

Standard solutions—Into separate 50-mL volumetric flasks, pipet 0.5, ~~1.5, 5, and 15 mL~~

■1.0, 1.5, and 3.0 mL■1S *(NF24)*
of the *Standard stock solution,* add 15.0 mL of *Buffer solution* to each volumetric flask, dilute with water to volume, and mix.

Test solution—Place about ~~1 g~~

■3 g■1S *(NF24)*
of Acesulfame Potassium, accurately weighed, in a 50-mL volumetric flask, dissolve in water, add 15.0 mL of *Buffer solution,* dilute with water to volume, and mix.

Procedure—Concomitantly measure the potential (see *Titrimetry* ⟨541⟩), in mV, of the *Standard solutions* and the *Test solution,* with a suitable pH meter equipped with a fluoride-specific ion electrode and a silver-silver chloride reference electrode. When taking the measurements, transfer the solution to a 25-mL beaker, and immerse the electrodes. Insert a polytef-coated stirring bar into the beaker, place the beaker on a magnetic stirrer having an insulated top, and allow to stir until equilibrium is attained (about 1 to 2 minutes). Rinse, and dry the electrodes between measurements, taking care not to scratch the crystal in the flouride-specific ion electrode. Measure the potential of each *Standard solution,* and plot the fluoride concentration, in µg per mL, versus the potential, in mV, on semilogarithmic paper. Measure the potential of the *Test solution,* and determine the fluoride concentration from the standard curve, in µg per mL. Calculate the percentage of fluoride in the portion of Acesulfame Potassium taken by the formula:

$$5(C/W),$$

in which C is the fluoride concentration, in µg per mL, from the standard curve; and W is the weight, in mg, of Acesulfame Potassium taken to prepare the *Test solution:* not more than 0.0003% of fluoride is found.

BRIEFING

Ethylcellulose Aqueous Dispersion, *NF 23* page 3004. It is proposed to remove the reference to the *Ethylcellulose* monograph, because the reference is invalid due to changes resulting from the harmonization process.

(ETM: J. Lane) RTS—42403-1

Change to read:

Identification—

A: Transfer a small quantity to a silver chloride plate, and allow the water to evaporate: the IR absorption spectrum of the residue in the 3600 to 2600 cm^{-1} and 1500 to 800 cm^{-1} regions exhibits maxima only at the same wave numbers as that of a film of USP Ethylcellulose RS prepared ~~as directed in the test for *Identification* under *Ethylcellulose.*~~

■by dissolving about 250 mg of USP Ethylcellulose RS in 5 mL of a mixture of 80 parts of toluene and 20 parts of alcohol and evaporating a few mL on a silver chloride plate.■1S *(NF24)*

B: Transfer about 2 mL to a 100-mm diameter petri dish so that the bottom of the dish is covered uniformly. Place the dish in an oven or on a hot plate to evaporate the water: a transparent film results.

In-Process Revision

C: Dissolve the film formed in *Identification* test *B* in 20 mL of chloroform. Inject 2 µL of this solution into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a 2-mm × 1.8-m column that contains 10% liquid phase G1 on support S1A maintained at a temperature of 220° and a flame-ionization detector. The temperatures of the injection port and the detector are maintained at about 250° and 275°, respectively. The retention time of the major peak following the solvent peak in the resulting chromatogram corresponds to that obtained from a similar solution of USP Cetyl Alcohol RS.

D: *Methylene blue solution*—To a 150-mL graduated beaker containing 0.7 mL of sulfuric acid and 5 g of anhydrous sodium sulfate slowly add water to the 90-mL mark. Add methylene blue solution (3 in 1000) to the 100-mL mark, and mix.

Procedure—To 1 mL of Aqueous Dispersion in a 100-mL graduated mixing cylinder add 9 mL of water followed by 25 mL of *Methylene blue solution*, and mix. Add 15 mL of chloroform, and shake vigorously. Allow the two phases to separate: the lower phase is blue, indicating the presence of sodium lauryl sulfate.

BRIEFING

Ethylparaben, *NF 23* page 3006 and page 3356 of the *First Supplement.* It is proposed to revise the *Melting range* in *Identification* test *B* to align the monograph with the harmonization text presented by the Pharmacopeial Discussion Group.

(EMC: J. Lane) RTS—42478-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: *Melting range* ⟨741⟩: ~~between 96° and 99°.~~

■between 115° and 118°.■IS (*NF24*)

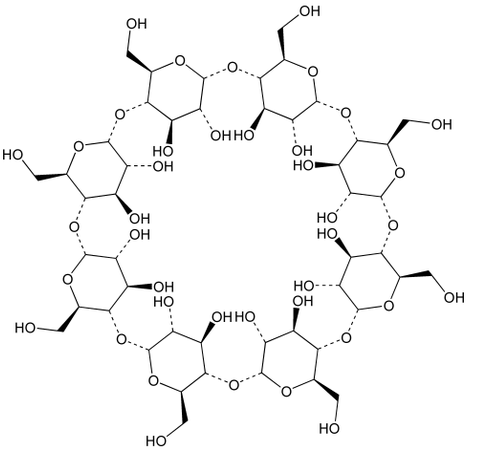
BRIEFING

Gamma Cyclodextrin. Because there is no existing *NF* monograph for this excipient, a new monograph, based on the manufacturer's tests and acceptance criteria, is being proposed. The liquid chromatographic procedures in the *Assay* were validated using a Nucleosil 100-5 NH_2, 4-mm × 25-cm brand of L8 column. The typical retention time for gamma cyclodextrin in the *Assay* is approximately 7.8 minutes. The liquid chromatographic procedures in the test for *Related compounds* were validated using a 4.6-mm × 25-cm Nucleosil 120-5 C18 brand of L1 column containing 5-µm packing and a 4.6-mm × 25-cm Supelcosil LC-18 brand of L1 column containing 5-µm packing. Typical retention times for gamma cyclodextrin, beta cyclodextrin, and alpha cyclodextrin in the test for *Related compounds* are approximately 3.2, 9.9, and 4.5 minutes, respectively.

(EMC: J. Lane; PSD: C. Okeke; NL: L. Paul; AMB: R. Tirumalai) RTS—41451-1

Add the following:

■Gamma Cyclodextrin



$C_{48}H_{80}O_{40}$ 1297.12 [*17465-86-0*].

» Gamma Cyclodextrin is composed of 8 gamma-(1–4) linked D-glycopyranosyl units. It contains not less than 98.0 percent and not more than 102.0 percent of $C_{48}H_{80}O_{40}$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

USP Reference standards ⟨11⟩—*USP Alpha Cyclodextrin RS. USP Beta Cyclodextrin RS. USP Gamma Cyclodextrin RS.*

In-Process Revision

Color and clarity of solution—

Test solution—Transfer about 2.5 g of Gamma Cyclodextrin, accurately weighed, into a 25-mL volumetric flask, dissolve in and dilute with water that 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: at 420 nm, the absorbance is not greater than 0.20; and the solution is clear.

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 test for *Specific rotation.*

Specific rotation ⟨781S⟩**:** between +174° and +180°.

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 microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Loss on drying ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 11.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%, determined on a 1.0-g specimen.

Heavy metals, *Method II* ⟨231⟩**:** 5 ppm.

Related compounds—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (90 : 10).

System suitability solution—Dissolve an accurately weighed quantity of USP Alpha Cyclodextrin RS, USP Beta Cyclodextrin RS, and USP Gamma Cyclodextrin RS in water to obtain a solution having a known concentration of about 0.5 mg of each per mL.

Standard solution—Transfer 25 mg of USP Gamma Cyclodextrin RS, accurately weighted, to a 25-mL volumetric flask, and dissolve in and dilute with water to volume.

Test solution—Dissolve about 250 mg of Gamma Cyclodextrin, previously dried, in water with the aid of heat. Cool, and dilute with water to 25.0 mL.

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 solution,* and record the peak responses as directed for *Procedure*: the retention time of gamma cyclodextrin is about 3.2 minutes; the relative retention times are about 1.4 for alpha cyclodextrin and about 3.1 for beta cyclodextrin; the resolution, *R,* between the alpha cyclodextrin and beta cyclodextrin peaks is not less that 1.5 and the resolution, *R,* between the beta cyclodextrin and gamma cyclodextrin peaks 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 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 alpha cyclodextrin are not greater than the area of the corresponding peaks in the chromatogram of the *Standard solution* (0.5%), and the sum of the areas of all the peaks, excluding the principal peak and the peaks corresponging to beta cy-

clodextrin or to alpha cyclodextrin, is not greater than half of the area of the peak corresponding to gamma cyclodextrin in the chromatogram of the *Standard solution* (0.5%).

Reducing substances—

Copper citrate solution—Dissolve, with the aid of heat, about 173 g of sodium citrate dihydrate and 117 g of sodium carbonate monohydrate in about 700 mL of water, and filter. In a second flask, dissolve about 27.06 g of cupric sulfate in about 100 mL of water. Slowly combine the two solutions while stirring, and dilute with water to 1000 mL.

Dextrose standard solution—Transfer 1.1 g of dextrose monohydrate, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with water to volume.

Procedure—Transfer about 1.0 g of Gamma Cyclodextrin, accurately weighed, to a 500-mL conical flask, dissolve in 10 mL of water, and add 25 mL of *Copper citrate solution*. Cover the flask with aluminum foil, and boil the solution for 5 minutes. Cool in an ice bath to room temperature. Add 25 mL of 0.6 N acetic acid, 10 mL of 3 N hydrochloric acid, and 10 mL of 0.1 N iodine solution. [NOTE—The addition of these solutions must be in the order given.] Titrate the solution with 0.1 N sodium thiosulfate VS, and determine the endpoint potentiometrically. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Create a calibration curve by similarly titrating 0.25, 0.5, 0.75, and 1.0 mL of *Dextrose standard solution*. Calculate the amount of reducing substances in the sample by comparing the thiosulfate consumption in the sample titration with that in the titration of the standard solutions of the calibration curve, and by dividing that amount by 10 to obtain the percentage: not more than 0.5% is found.

Organic volatile impurities *Method IV* ⟨467⟩**:** meets the requirements.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (67 : 33).

Standard preparation—Dissolve an accurately weighed quantity of USP Gamma Cyclodextrin RS in water to obtain a solution having a known concentration of about 10 mg per mL.

Assay preparation—Transfer about 100 mg of Gamma Cyclodextrin, previously dried, to a 10-mL volumetric flask, and dissolve in about 8 mL of water. Dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 4-mm × 25-cm column that contains 10-µm packing L8. The flow rate is about 1.0 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 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 $C_{48}H_{80}O_{40}$ in the portion of Gamma Cyclodextrin taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Gamma Cyclodextrin 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 (*NF24*)

In-Process Revision

BRIEFING

Maleic Acid, *NF 23* page 3031. It is proposed to make a correction in the *Identification* test *A*.

(EMC: E. Gonikberg) RTS—42378-1

Change to read:

Identification—

A: Dissolve about 500 mg of Maleic Acid in 10 mL of water: the pH of the solution is ~~not~~

■■1S (*NF24*)
less than 2.

B: The principal spot in the chromatogram obtained from *Test solution 2* corresponds in color, size, and R_F value to that in the chromatogram obtained from the *Maleic acid standard solution,* as obtained in the test for *Limit of fumaric acid.*

C: Dissolve about 35 mg of resorcinol in 10 mL of sulfuric acid *(Resorcinol solution).* Dissolve about 100 mg of Maleic Acid in 10 mL of water *(Test solution).* To 0.3 mL of the *Test solution* add 3 mL of the *Resorcinol solution,* and heat in a water bath for 15 minutes: no color develops. To 3 mL of the *Test solution* add 1 mL of bromine TS, heat in a water bath for 15 minutes to remove the bromine, then heat to boiling, and cool. To 0.2 mL of this solution, add 3 mL of the *Resorcinol solution,* and heat in a water bath for 15 minutes: a violet-pink color develops.

BRIEFING

Maltose, *NF 23* page 3034 and page 3358 of the *First Supplement.* On the basis of comments received, it is proposed to revise the lower limit in the test for *Water* from 5.0% to 4.5%.

(EMC: C. Sheehan) RTS— 42452-1

Change to read:

Water, *Method I* ⟨921⟩—The anhydrous form contains not more than 1.5%. The monohydrate form contains not less than ~~5.0%~~

■4.5%■1S (*NF24*)
and not more than 6.5%.

BRIEFING

Olive Oil, *NF* 23 page 3043. Based on comments received, it is proposed to revise the test for *Teaseed oil* regarding the interpretation of a color reaction in the test. It is proposed to include a *Note* concerning a pink coloration based on the text adopted in the seventh session report of the Joint FAO/WHO Codex Alimentarius Commission. It is also proposed to revise the Definition and add a *Labeling* section to include the use of suitable antioxidants.

(EMC: C. Sheehan; NL: L. Paul) RTS—42427-1

Change to read:

» Olive Oil is the fixed oil obtained from the ripe fruit of *Olea europaea* Linné (Fam. Oleaceae).

■It may contain suitable antioxidants.■1S (*NF24*)

Add the following:

■**Labeling**—Label it to indicate the name and quantity of any suitable antioxidants.■1S (*NF24*)

Change to read:

Teaseed oil—In a dry, 18- × 150-mm test tube place 0.8 mL of acetic anhydride, 1.5 mL of chloroform, and 0.2 mL of sulfuric acid, mix, and cool in a water bath to 25°. Add about 200 mg of Olive Oil (about 7 drops), mix, and cool to 25°. If the solution is cloudy, add acetic anhydride, dropwise, shaking after each addition, until the solution suddenly clears. Allow the mixture to remain in the water bath for 5 minutes: it shows a green color by both reflected and transmitted light. Add 10 mL of absolute ether, and mix by inverting the tube: the initial green color fades to a brownish gray. (Before the dilution with ether, the presence of *teaseed oil* will cause a brown color to appear by transmitted light, and after the dilution, a transient red color.)

■[NOTE—A pink color is regarded as negative, because some olive oils yield this color.]■1S (*NF24*)

BRIEFING

Phenoxyethanol, *NF 23* page 3048. It is proposed to correct the calculations in the *Assay* and add a clarification under *Chromatographic purity* test. The proposals to add the test for *Bacterial endotoxins,* and the *Labeling* and *Reference standards* proposals related to this addition, published on page 94 of *PF* 31(1) [Jan.–Feb. 2005], are now being canceled.

(EMC: E. Gonikberg) RTS—42458-1

Change to read:

Chromatographic purity—

Phenol solution—Prepare a solution of phenol in isopropyl alcohol having a known concentration of about 0.25 mg of phenol per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Phenoxyethanol RS in *Phenol solution* to obtain a solution having a known concentration of about 5 mg of phenoxyethanol per mL. Accurately transfer 500 µL of this solution to a vial, add 1000 µL of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 seconds.

■Calculate the concentrations of phenoxyethanol and phenol in this solution.■1S (*NF24*)

Test solution—Accurately transfer 500 µL of Phenoxyethanol to a tared vial, and determine the weight of Phenoxyethanol taken. Add 1000 µL of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 seconds.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 10-m capillary column coated with a 5-µm film of stationary phase G27. The carrier gas is helium with a split flow rate of 44 mL per minute. The injector port temperature and the detector temperature are both maintained at 300°. The column temperature is programmed as follows: the starting column temperature is 80°; after injection, it is increased to 260° at a rate of 8° per minute, then held for 10 minutes. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between phenol and phenoxyethanol peaks is not less than 10; and the relative standard deviation for replicate injections for the phenoxyethanol peak is not more than 2.0%.

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 area responses. Calculate the percentage of total impurities in the portion of Phenoxyethanol taken by the formula:

$$150(C/W)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of phenoxyethanol in the *Standard solution; W* is the weight of Phenoxyethanol, in mg, taken to prepare the *Test solution;* r_U is the sum of all additional peak areas in the chromatogram obtained from the *Test solution,* excluding the main peak, the solvent peak, and the phenol peak; and r_S is the peak area of the phenoxyethanol peak in the chromatogram obtained from the *Standard solution:* not more than 1.0% of total impurities is found.

Change to read:

Assay—

Phenol solution and *Chromatographic system*—Prepare as directed under *Chromatographic purity.*

Standard preparation—Use the *Standard solution,* prepared as directed under *Chromatographic purity.*

Assay preparation—Transfer about 500 mg of Phenoxyethanol, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with isopropyl alcohol to volume, and mix. Accurately transfer 500 µL of this solution to a vial, add 1000 µL of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 seconds.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the quantity, in mg, of $C_8H_{10}O_2$ in the portion of Phenoxyethanol taken by the formula:

~~$150C(r_u / r_s),$~~

$$■300C(r_U / r_S),■1S\ (NF24)$$

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

BRIEFING

Polyoxyl 10 Oleyl Ether, *NF 23* page 3058 and **Polyoxyl 20 Cetostearyl Ether,** *NF 23* page 3059. It is proposed to revise the *Standard preparation* in the test for *Free ethylene oxide* to remove the requirement to use USP Reference Standard material as the diluent for the ethylene oxide. It is sufficient to use the sample under test to prepare the *Standard preparation*.

(EMC: K. Russo) RTS—42354-1

Change to read:

Free ethylene oxide—

Internal standard solution—Prepare a solution containing 100 mg of *n*-butyl chloride in each mL of chlorobenzene. Store in a tightly closed container. Prepare fresh weekly.

Standard solution—[Caution—Ethylene oxide is toxic and flammable. Prepare this solution in a well-ventilated hood, using great care.] Place 250 mL of chlorobenzene in a glass-stoppered, 500-mL conical flask. Bubble ethylene oxide through the chlorobenzene at a moderate rate for about 30 minutes, insert the stopper,

In-Process Revision

and store with protection from heat. Pipet 25 mL of a 0.5 N alcoholic hydrochloric acid solution, prepared by mixing 45 mL of hydrochloric acid with 1 L of alcohol, into a 500-mL conical flask containing 40 g of magnesium chloride hexahydrate. Shake the mixture to effect saturation. Pipet 10 mL of the ethylene oxide solution into the flask, and add 20 drops of bromocresol green TS. If the solution is not yellow (acid) at this point, add an additional volume, accurately measured, of 0.5 N alcoholic hydrochloric acid to give an excess of about 10 mL. Record the total volume of 0.5 N alcoholic hydrochloric acid added. Insert the stopper in the flask, and allow to stand for 30 minutes. Titrate the excess acid with 0.5 N alcoholic potassium hydroxide VS. Perform a blank titration, using 10.0 mL of chlorobenzene instead of ethylene oxide solution, adding the same total volume of 0.5 N alcoholic hydrochloric acid, and note the difference in volumes required. Each mL of the difference in volumes of 0.5 N alcoholic potassium hydroxide consumed is equivalent to 22.02 mg of ethylene oxide. Calculate the concentration, in mg per mL, of ethylene oxide in the *Standard solution*. Standardize daily.

Standard preparation—Transfer about 5 g of ~~USP Polyoxyl 10 Oleyl Ether RS~~

■Polyoxyl 10 Oleyl Ether■1S (*NF24*)
to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene, exactly 50 µL of *Internal standard solution,* and an accurately measured volume of *Standard solution* containing about 0.5 mg of ethylene oxide. Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Test preparation—Transfer about 5 g of Polyoxyl 10 Oleyl Ether, accurately weighed, to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene and 50 µL, accurately measured, of *Internal standard solution*.

■Add a volume of chlorobenzene equal to the volume of the *Standard solution* added to prepare the *Standard preparation.*■1S (*NF24*)
Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Chromatographic system—Under typical conditions, the instrument is equipped with a flame-ionization detector, and contains a 3-mm (OD) × 1.8-m stainless steel column packed with S3. The injector port and detector block temperatures are maintained at about 210° and 230°, respectively, and the column temperature at about 160°. Helium is used as the carrier gas at a flow rate of 66 mL per minute.

Interference check—Inject a suitable volume of chlorobenzene into the gas chromatograph, and allow the chromatogram to run until the solvent has eluted. Similarly inject and chromatograph the *Internal standard solution*, the *Standard solution,* and a solution prepared according to the directions for the *Test preparation,* but omitting the internal standard. No interfering peaks are observed.

Procedure—Inject about 2 µL of the *Standard preparation* into a suitable gas chromatograph, and record the chromatogram. Similarly, inject about 2 µL of the *Test preparation,* and record the chromatogram. ~~Calculate the quantity, in mg, of ethylene oxide in the portion of Polyoxyl 10 Oleyl Ether taken by the formula:~~

~~$W_E(R_U / R_S)$,~~

~~in which W_E is the weight, in mg, of ethylene oxide in the portion of *Standard solution* taken, and R_U and R_S are the area ratios of ethylene oxide to internal standard in the chromatograms for the *Test preparation* and the *Standard preparation*, respectively. The limit is 0.01%.~~

■Calculate the weight, in g, of ethylene oxide in the *Test preparation* (W_T) by the formula:

$$(W_E W_U R_U)/1000(W_U R_S - W_S R_U),$$

in which W_E is the weight, in mg, of ethylene oxide added to the *Standard preparation;* W_U and W_S are the weights, in g, of Polyoxyl 10 Oleyl Ether used to prepare the *Test preparation* and the *Standard preparation,* respectively; and R_U and R_S are the area ratios of ethylene oxide to internal standard in the chromatograms for the *Test preparation* and the *Standard preparation,* respectively. Calculate the percentage of ethylene oxide in the portion of Polyoxyl 10 Oleyl Ether taken by the formula:

$$100W_T / W_U,$$

in which W_T and W_U are as defined previously. The limit is 0.01%.■1S (*NF24*)

BRIEFING

Polyoxyl 20 Cetostearyl Ether, *NF 23* page 3059—See briefing under *Polyoxyl 10 Oleyl Ether.*

(EMC: K. Russo) RTS—42354-2

Change to read:

Free ethylene oxide—

Internal standard solution—Prepare a solution containing 100 mg of *n*-butyl chloride in each mL of chlorobenzene. Store in a tightly closed container. Prepare fresh weekly.

Standard solution—[Caution—Ethylene oxide is toxic and flammable. Prepare this solution in a well-ventilated hood, using great care.] Place 250 mL of chlorobenzene in a glass-stoppered, 500-mL conical flask. Bubble ethylene oxide through the chlorobenzene at a moderate rate for about 30 minutes, insert the stopper, and store protected from heat. Pipet 25 mL of 0.5 N alcoholic hy-

drochloric acid solution, prepared by mixing 45 mL of hydrochloric acid with 1 L of alcohol, into a 500-mL conical flask containing 40 g of magnesium chloride hexahydrate. Shake the mixture to effect saturation. Pipet 10 mL of the ethylene oxide solution into the flask, and add 20 drops of bromocresol green TS. If the solution is not yellow (acid) at this point, add an additional volume, accurately measured, of 0.5 N alcoholic hydrochloric acid to give an excess of about 10 mL. Record the total volume of 0.5 N alcoholic hydrochloric acid added. Insert the stopper in the flask, and allow to stand for 30 minutes. Titrate the excess acid with 0.5 N alcoholic potassium hydroxide VS. Perform a blank titration, using 10.0 mL of chlorobenzene instead of ethylene oxide solution, adding the same total volume of 0.5 N alcoholic hydrochloric acid, and note the difference in volumes required. Each mL of the difference in volumes of 0.5 N alcoholic potassium hydroxide consumed is equivalent to 22.02 mg of ethylene oxide. Calculate the concentration, in mg per mL, of ethylene oxide in the *Standard solution*. Standardize daily.

Standard preparation—Transfer about 5 g of ~~USP Polyoxyl 20 Cetostearyl Ether RS~~

■Polyoxyl 20 Cetostearyl Ether ■1S (*NF24*)
to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene, exactly 50 µL of *Internal standard solution,* and an accurately measured volume of *Standard solution* containing about 0.5 mg of ethylene oxide. Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Test preparation—Transfer about 5 g of Polyoxyl 20 Cetostearyl Ether, accurately weighed, to a suitable glass bottle of about 60-mL capacity, and add 10 mL of chlorobenzene and 50 µL, accurately measured, of *Internal standard solution*.

■Add a volume of chlorobenzene equal to the volume of the *Standard solution* added to prepare the *Standard preparation*. ■1S (*NF24*)
Insert a magnetic stirring bar, cap the bottle tightly, and stir until homogeneity is attained.

Chromatographic system—Under typical conditions, the instrument is equipped with a flame-ionization detector, and contains a 3-mm (OD) × 1.8-m stainless steel column packed with S3. The injector port and detector block temperatures are maintained at about 210° and 230°, respectively, and the column temperature at about 160°. Helium is used as the carrier gas at a flow rate of 66 mL per minute.

Interference check—Inject a suitable volume of chlorobenzene into the gas chromatograph, and allow the chromatogram to run until the solvent has eluted. Similarly inject and chromatograph the *Internal standard solution,* the *Standard solution,* and a solution prepared according to the directions for the *Test preparation,* but omitting the internal standard. No interfering peaks are observed.

Procedure—Inject about 2 µL of the *Standard preparation* into a suitable gas chromatograph, and record the chromatogram. Similarly, inject about 2 µL of the *Test preparation*, and record the chromatogram. ~~Calculate the quantity, in mg, of ethylene oxide in the portion of Polyoxyl 20 Cetostearyl Ether taken by the formula:~~

~~$W_S(R_U / R_S)$,~~

~~in which W_S is the weight, in mg, of ethylene oxide in the portion of *Standard solution* taken, and R_U and R_S are the area ratios of ethylene oxide to internal standard in the chromatograms for the *Test preparation* and the *Standard preparation*, respectively. The limit is 0.01%.~~

■Calculate the weight, in g, of ethylene oxide in the *Test preparation* (W_T) by the formula:

$$(W_E W_U R_U)/1000(W_U R_S - W_S R_U),$$

in which W_E is the weight, in mg, of ethylene oxide added to the *Standard preparation*; W_U and W_S are the weights, in g, of Polyoxyl 20 Cetostearyl Ether used to prepare the *Test preparation* and the *Standard preparation*, respectively; and R_U and R_S are the area ratios of ethylene oxide to internal standard in the chromatograms for the *Test preparation* and the *Standard preparation*, respectively. Calculate the percentage of ethylene oxide in the portion of Polyoxyl 20 Cetostearyl Ether taken by the formula:

$$100 W_T / W_U,$$

in which W_T and W_U are as defined previously. The limit is 0.01%. ■1S (*NF24*)

BRIEFING

Sodium Benzoate, *NF 23* page 3075. It is proposed to add a spectrophotometric identification test to this monograph employing *Infrared Absorption* ⟨197M⟩ and to include a new Reference Standard, USP Sodium Benzoate RS, to be used to perform this test.

(EMC: C. Sheehan) RTS—42426-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Sodium Benzoate RS*. ■1S (*NF24*)

In-Process Revision

Change to read:

Identification—

■**A:** *Infrared Absorption* ⟨197M⟩, on the undried specimen.

B: ■1S (*NF24*)
It responds to the tests for *Sodium* ⟨191⟩ and for *Benzoate* ⟨191⟩.

BRIEFING

Tagatose, page 1672 of *PF* 30(5) [Sept.–Oct. 2004]. On the basis of comments received, it is proposed to widen the proposed range for *Specific rotation,* to accommodate the high-purity material currently available on the market. It is also proposed to clarify the description of the atomic absorption spectrophotometer used in the test for *Lead*. The liquid chromatographic procedure in the *Assay* was validated using a Biorad Aminex HPX-87C brand of L19 column; tagatose peak elutes at approximately 16 minutes.

(EMC: E. Gonikberg) RTS—42394-1; 42394-2

BRIEFING

Sugar Spheres, *NF 23* page 3096. It is proposed to revise the *Identification* test because there is an incorrect cross reference to the deleted *Starch* monograph.

(EMC: R. Ravichandran) RTS—42391-1

Change to read:

Identification—~~Transfer about 20 g, accurately weighed, to a 200-mL volumetric flask, add 160 mL of water, shake to dissolve the sucrose, add water to volume, and mix. Separate the solubilized sucrose from the insoluble starch component by vacuum filtration through fine filter paper until the filtrate is clear. A water slurry of the insoluble portion responds to *Identification*test *B* under *Starch.* [NOTE—Use the freshly prepared, clear filtrate for the *Specific rotation* test.].~~

■A 1 : 10 suspension gives a violet to deep blue color with iodine TS.■1S (*NF24*)

Change to read:

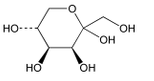
Specific rotation ⟨781⟩: not less than +41° and not more than +61°, ~~determined on a portion of the filtrate obtained in the *Identification* test,~~

■■1S (*NF24*)
corresponding to not less than 62.5% and not more than 91.5% of sucrose ($C_{12}H_{22}O_{11}$), calculated on the dried basis.

■*Test solution*—Transfer about 20 g accurately weighed, to a 200-mL volumetric flask, add 160 mL of water, shake to dissolve the sucrose, add water to volume, and mix. Pass the solubilized sucrose solution by vacuum filtration through fine filter paper.■1S (*NF24*)

Add the following:

■Tagatose



$C_6H_{12}O_6$ 180.16 [*87-81-0*].

D-Tagatose.

D-*lyxo*-Hexulose.

» Tagatose is a ketohexose, an epimer of D-fructose inverted at C-4. It is obtained from D-galactose by isomerization under alkaline conditions in the presence of calcium. It contains not less than 98.0 percent of $C_6H_{12}O_6$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

USP Reference standards ⟨11⟩**—***USP Tagatose RS.*

In-Process Revision

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: Add 3 mL of a solution (1 in 5) to 5 mL of hot alkaline cupric tartrate TS: a copious red precipitate of cuprous oxide is formed.

Melting range, *Class 1* ⟨741⟩**:** between 133° and 144°.

Specific rotation ⟨781S⟩**:** ~~between 4° and 5.6°.~~ between –4° and –7°.

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 microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Loss on drying ⟨731⟩—Dry it at 102° for 2 hours: it loses not more than 0.5% of its weight.

Total ash ⟨561⟩**:** not more than 0.1%, determined on a 1.0-g specimen.

Limit of lead—

Test solution—Accurately weigh about 2.5 g of Tagatose, and dissolve in a mixture of 4 mL of sulfuric acid and 5 mL of hydrochloric acid. Transfer the solution to a 50-mL volumetric flask, dilute with water to volume, and mix.

Standard lead solution—Dissolve 1.60 g of lead nitrate in diluted nitric acid (10 mL of nitric acid diluted with 20 mL water, boiled to remove nitrous fumes, and cooled), and dilute with water to 1000 mL. Dilute 10.0 mL of this solution with water to 500 mL. This solution contains the equivalent of 20 µg of lead per mL.

Calibration solutions—To a series of 100-mL volumetric flasks, pipet 0, 1, 2, 3, 4 and 5 mL of the *Standard lead solution,* and dilute to about 50 mL. Add 8 mL of sulfuric acid and 10 mL of hydrochloric acid to each flask, shake to dissolve, and dilute with water to volume. These solutions contain 0, 0.2, 0.4, 0.6, 0.8 and 1.0 µg of lead per mL.

Procedure—Concomitantly determine the absorbances of the *Calibration solutions* and the *Test solution* at the wavelength of maximum absorbance at 283.3 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩). ~~using an air–acetylene flame~~ Plot the absorbances of the *Calibration solutions* versus the concentration of lead. Using this graph, determine the concentration of lead in the *Test solution.* Not more than 1 µg per g is found.

Assay—

Mobile phase—Prepare a solution in water containing 50 mg of calcium acetate per L.

Standard preparation—Dissolve an accurately weighed quantity of USP Tagatose RS in water to obtain a solution having a known concentration of about 5 mg per mL. Pass through a 0.2-µm filter.

Assay preparation—Transfer about 50 mg of Tagatose, previously dried, to a 10-mL volumetric flask, and dissolve in about 8 mL of water. Dilute with water to volume, and pass through a 0.2-µm filter.

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 9-µm packing L19. The column temperature is maintained at 85°. The flow rate is about 0.6 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%.

In-Process Revision

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 $C_6H_{12}O_6$ in the portion of Tagatose taken by the formula:

$$10C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Tagatose 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 (*NF24*)

Change to read:

Identification—

A: ~~Triturate it with about an equal weight of camphor or menthol: the mixture liquefies.~~

■*Infrared Absorption* ⟨197K⟩.■1S (*NF24*)

B: ~~Dissolve a very small crystal of it in 1 mL of glacial acetic acid, and add 6 drops of sulfuric acid and 1 drop of nitric acid: the liquid shows a deep bluish green color when viewed by reflected light.~~

■It meets the requirements under *Melting range.*■1S (*NF24*)

~~**C:** Place about 1 g in a test tube, add 5 mL of sodium hydroxide solution (1 in 10), and heat in a water bath: a clear, colorless or pale red, solution is produced, and it becomes darker on standing, without the separation of oily drops. Add to this solution a few drops of chloroform, and agitate the mixture: a violet color is produced.~~

■■1S (*NF24*)

BRIEFING

Thymol, *NF* 23 page 3098. It is proposed to delete the current *Identification* tests *A, B,* and *C* and replace them with two new identification tests: a spectrophotometric identification test employing *Infrared Absorption* ⟨197K⟩ and a test that meets the monograph requirements under *Melting Range* ⟨741⟩; a new Reference Standard, USP Thymol RS, is also proposed to be used in *Identification* test *A*.

(EMC: C. Sheehan) RTS—42428-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Thymol RS.*■1S (*NF24*)

BRIEFING

Xanthan Gum, *NF 23* page 3108. It is proposed to revise the *Assay* to specify the procedure under the general test chapter *Alginates Assay* ⟨311⟩, including *System Suitability.*

(EMC: R. Ravichandran) RTS—42399-1

Change to read:

Assay—Proceed as directed ~~with Xanthan Gum for *Procedure*~~

■■1S (*NF24*)
under *Alginates Assay* ⟨311⟩ using about 1.2 g of Xanthan Gum, accurately weighed.

In-Process Revision

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 28* page 2204, page 3290 of the *First Supplement,* the *First Interim Revision Announcement* on page 33 of *PF* 31(1) [Jan.–Feb. 2005], the *Second Interim Revision Announcement* on page 357 of *PF* 31(2) [Mar.–Apr. 2005], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 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 710 of *PF* 29(3) [May–June 2003], page 1137 of *PF* 29(4) [July–Aug. 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 998 of *PF* 30(3) [May–June 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], and page 507 of *PF* 31(2) [Mar.–Apr. 2005].

(HDQ) RTS—41008-2; 41225-1; 41730-1; 41225-1; 41672-1; 41684-1; 41833-1; 41833-3; 41833-5; ; 42222-1; 42290-1; 42426-1; 42428-1

In-Process Revision

Add the following:

■**USP Aprotinin RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Aprotinin System Suitability RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Bicalutamide RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Bicalutamide Related Compound A RS [***N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfinyl]-2-hydroxy-2-methylpropanamide**]** ($C_{18}H_{14}F_4N_2O_3S$ ✧ 414.38)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Hydrobromide RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound A RS [**1-(3-dimethylaminopropyl)-1-(4′-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide**]** ($C_{20}H_{23}FN_2O_2$ ✧ 342.22)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound B RS [**1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile**]** ($C_{20}H_{21}FN_2O_2$ ✧ 340.22)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound C RS [**3-(3-*N,N*-dimethylamino)-1-(4-fluorophenyl)-6-cyano-1(3*H*)-isobenzofuranone**]** ($C_{20}H_{19}FN_2O_2$ ✧ 338.22)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound D RS [**1-(4-fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile**]** ($C_{19}H_{19}FN_2O$ ✧ 310.21)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound E RS [**1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile-*N*-oxide**]** ($C_{20}H_{21}FN_2O_2$ ✧ 340.22)—[To come.]■1S (*USP29*)

Add the following:

■**USP Citalopram Related Compound F RS [**dimethyl-(1-methyl-3,3-diphenyl-allyl)-amine hydrochloride**]** ($C_{18}H_{21}NHCl$ ✧ 286.64)—[To come.]■1S (*USP29*)

Add the following:

■**USP Drospirenone RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Fenofibrate RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Fenofibrate Related Compound A RS [** (4-chlorophenyl)(4-hydroxyphenyl)methanone **]**—[To come.]■1S (*USP29*)

Add the following:

■**USP Fenofibrate Related Compound B RS [**2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, or fenofibric acid**]**—[To come.]■1S (*USP29*)

Add the following:

■**USP Fenofibrate Related Compound C RS [**1-methylethyl 2-[[2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoyl]oxy]-2-methylpropanoate**]**—[To come.]■1S (*USP29*)

Add the following:

■**USP Glyburide Related Compound A RS [**(4-[2-(5-chloro-2-methoxybenzamido)ethyl[benzenesulfonamide**]**—[To come.]■1S (*USP29*)

Add the following:

■**USP Metformin Related Compound B RS [**1-methylbiguanide**]** ($C_3H_9N_5$ ✧ 115.14)—[To come.]■1S (*USP29*)

Add the following:

■**USP Metformin Related Compound C RS [**dimethylmelamine, or *N,N*-dimethyl-[1,3,5]triazine-2,4,6-triamine**]** ($C_5H_{10}N_6$ ✧ 154.17)—[To come.]■1S (*USP29*)

Add the following:

■**USP Ritonavir RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Ritonavir Related Compounds Mixture RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Sodium Benzoate RS**—[To come.]■1S (*USP29*)

Add the following:

■**USP Thymol RS**—[To come.]■1S (*USP29*)

Physical Tests and Determinations

BRIEFING

⟨**611**⟩ **Alcohol Determination,** *USP 28* page 2378 and page 1379 of *PF* 30(4) [July–Aug. 2004]. It is proposed to revise *Method II* to add a new capillary gas chromatographic method, *Method IIb,* developed and validated by USP laboratories. The new method was validated using a DB-624 column, a brand name of G43 column, manufactured by J&W Scientific. The official *Method II* is now designated as *Method IIa.* Manufacturers interested in incorporating *Method IIb* in compendial monographs are encouraged to submit appropriate requests for revision with supporting documentation.

(PA2: H. Pappa) RTS—42355-1

Change to read:

METHOD II—GAS ~~LIQUID~~

■■1S (*USP29*)

CHROMATOGRAPHIC METHOD

~~Method II is to be used where~~

■Use *Method IIa* when *Method II* is■1S (*USP29*) specified in the individual monograph. For a discussion of the principles upon which it is based, see *Gas Chromatography* under *Chromatography* ⟨621⟩.

In-Process Revision

▲**USP Reference Standards**—*USP Alcohol Determination—Acetonitrile RS. USP Alcohol Determination—Alcohol RS.* ▲*USP28*

■Method IIa■1S (*USP29*)

Apparatus—Under typical conditions, use a gas chromatograph equipped with a flame-ionization detector and a 4-mm × 1.8-m 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—

▲*USP28*

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 ▲5 mL each of the *Test Stock Preparation* and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 50-mL▲*USP28* volumetric flask, and dilute with water to volume.

Standard Preparation—Pipet ▲5 mL each of the USP Alcohol Determination—Alcohol RS and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 50-mL▲*USP28* 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:

$$\blacktriangle CD(R_U / R_S),\ \blacktriangle USP28$$

in which ▲C is the labeled concentration of USP Alcohol Determination—Alcohol RS;▲*USP28* 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;~~

■2.0;■2S (*USP28*)

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.

■Method IIb

Apparatus—The gas chromatograph is equipped with a split injection port with a split ratio of 5 : 1, a flame-ionization detector, and a 0.53-mm × 30-m capillary column coated with a 3.0-µm film of phase G43. Helium is used as the carrier gas at a linear velocity of 34.0 cm per second. The chromatograph is programmed to maintain the column temperature at 50° for 5 minutes, then to increase the temperature at a rate of 10° per minute to 200°, and held at this temperature for 4 minutes. The injection port is maintained at 210° and the detector temperature at 280°.

Solutions—

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 5 mL each of the *Test Stock Preparation* and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution.] into a 25-mL volumetric flask, and dilute with water to volume.

Standard Preparation—Pipet 5 mL each of the USP Alcohol Determination—Alcohol RS and USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution.] into a 25-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Inject about 0.2 µL each of the *Test Preparation* and the *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:

$$CD(R_U / R_S),$$

in which C is the labeled concentration of USP Alcohol Determination—Alcohol RS; D is the dilution factor (the ratio of the volume of the *Test Stock Preparation* to the volume of

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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*, between alcohol and the internal standard is not less than 4; six replicate injections of the *Standard Preparation* show a relative standard deviation of not more than 4.0% in the ratio of the peak of alcohol to the peak of the internal standard; and the tailing factor of the alcohol peak is not greater than 2.0.■1S (*USP29*)

BRIEFING

⟨**621**⟩ **Chromatography,** *USP 28* page 2380, page 3317 of the *First Supplement,* and page 2094 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to revise the *System Suitability* section to clarify the requirements for verification of system suitability following adjustments in operating conditions. In this regard, a reference to the proposed new general information chapter *Verification of Compendial Procedures* ⟨1226⟩ (see page 555 of *PF* 31(2) [Mar.–Apr. 2005]) has been added. It is also proposed to clarify that relative retention times in monographs are given for informational purposes only and that there are no acceptance criteria associated with these values. Also, in the *Chromatographic Reagents* section, it is proposed to eliminate the footnotes and to replace them with *Notes* inserted in the text after the corresponding column designations.

(PA2: H. Pappa; BPC: M. Marques) RTS—42312-1; 42331-1; 42332-1

Change to read:

INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic ~~tests and assays of~~

■procedures for■2S (*USP28*)
drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus ~~obtained~~

■separated■2S (*USP28*)
can be identified or determined by analytical ~~methods.~~

■procedures.■2S (*USP28*)
The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the "eluant." The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina ~~, silica gel, and ion-exchange resins,~~

■and silica gel,■2S (*USP28*)
or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. ~~In the latter process, a liquid coating held on an inert support serves as the stationary phase.~~

■In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the wall of a fused silica capillary, serves as the stationary phase.■2S (*USP28*)
Partitioning is the predominant mechanism of separation in gas–liquid chromatography, paper chromatography, and forms of column chromatography

■and thin-layer chromatography■2S (*USP28*)
designated as liquid-liquid ~~chromatography.~~

■separation.■2S (*USP28*)
In practice, separations frequently result from a combination of adsorption and partitioning effects.

■Other separation principles include ion exchange, ion-pair formation, size exclusion, hydrophobic interaction, and chiral recognition.■2S (*USP28*)
The types of chromatography useful in qualitative and quantitative analysis that are employed in the *USP* ~~tests and assays~~

■procedures■2S (*USP28*)
are column, gas, paper, thin-layer,

■(including high-performance thin-layer chromatography),■2S (*USP28*)
and pressurized liquid chromatography (commonly called high-pressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification, because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. ~~Both gas chromatography and pressurized liquid chromatography require more elaborate apparatus and usually provide high resolution methods that will identify and quantitate very small amounts of material.~~

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■Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material.■2S (*USP28*)

Use of Reference Substances in Identity Tests—In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot

■or zone)■2S (*USP28*)
traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the R_F value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the R_R value. R_F values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and R_F value and the mixed chromatogram yields a single spot; i.e., R_R is 1.0.

Location of Components—The spots produced by paper or thin-layer chromatography may be located by: (1) direct inspection if the compounds are visible under white or either short-wavelength (254 nm) or long-wavelength (360 nm) UV light, (2) inspection in white or UV light after treatment with reagents that will make the spots visible (reagents are most conveniently applied with an atomizer), (3) use of a Geiger-Müller counter or autoradiographic techniques in the case of the presence of radioactive substances, or (4) evidence resulting from stimulation or inhibition of bacterial growth by the placing of removed portions of the adsorbent and substance on inoculated media.

In open-column chromatography, in pressurized liquid chromatography performed under conditions of constant flow rate, and in gas chromatography, the retention time, *t,* defined as the time elapsed between sample injection and appearance of the peak concentration of the eluted sample zone, may be used as a parameter of identification. Solutions of the substance to be identified or derivatives thereof, of the reference compound, and of a mixture of equal amounts of these two are chromatographed successively on the same column under the same chromatographic conditions. Only one peak should be observed for the mixture. The ratio of the retention times of the test substance, the reference compound, and a mixture of these, to the retention time of an internal standard is called the relative retention time R_R and is also used frequently as a parameter of identification.

The deviations of R_R, R_F, or t values measured for the test substance from the values obtained for the reference compound and mixture should not exceed the reliability estimates determined statistically from replicate assays of the reference compound.

Chromatographic identification by these methods under given conditions strongly indicates identity but does not constitute definitive identification. Coincidence of identity parameters under 3 to 6 different sets of chromatographic conditions (temperatures, column packings, adsorbents, eluants, developing solvents, various chemical derivatives, etc.) increases the probability that the test and reference substances are identical. However, many isomeric compounds cannot be separated. Specific and pertinent chemical, spectroscopic, or physicochemical identification of the eluted component combined with chromatographic identity is the most valid criterion of identification. For this purpose, the individual components separated by chromatography may be collected for further identification.

Change to read:

THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an ''open chromatographic column'' and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of ~~support,~~

■stationary phase,■2S (*USP28*)
its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange ~~films~~

■layers■2S (*USP28*)
can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots

■or zones■2S (*USP28*)
of identical R_F value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size ~~of the spots~~

■or intensity of the spots or zones■2S (*USP28*)
may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry ~~, fluorescence, and fluorescence quenching;~~

■(absorbance or fluorescence measurements),■2S (*USP28*)
or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus—Acceptable apparatus and materials for thin-layer chromatography consist of the following.

~~Flat *glass plates* of convenient size, typically 20 cm × 20 cm.[*]~~

~~An *aligning tray* or a flat surface upon which to align and rest the plates during the application of the adsorbent.~~

~~A *storage rack* to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.~~

~~The *adsorbent* consists of finely divided adsorbent materials, normally 5 to 40 µm in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of paris (hydrated calcium sulfate) [at a ratio of 5% to 15%] or with starch paste or other binders. The former will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb ultraviolet light.~~

~~A *spreader,* which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate.~~

~~[*] Commercially prepared plates may be substituted for plates prepared as directed herein.~~

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~~A *developing chamber* that can accommodate one or more plates and can be properly closed and sealed as described under *Ascending Chromatography.* The chamber is fitted with a *plate-support rack* that supports the plates, back to back, with the lid of the chamber in place.~~

~~A *template* (generally made of plastic) to aid in placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates.~~

~~A graduated *micropipet* capable of delivering 10 µL volumes. Total volumes of test and standard solutions are specified in the individual monograph.~~

~~A *reagent sprayer* that will emit a fine spray and will not itself be attacked by the reagent.~~

~~An *ultraviolet light source* suitable for observations with short (254 nm) and long (360 nm) UV wavelengths.~~

■A *TLC or HPTLC plate.* The chromatography is generally carried out using *precoated plates* or *sheets* (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at 120° for 20 minutes. The *stationary phase* of TLC plates has an average particle size of 10–15 µm, and that of HPTLC plates an average particle size of 5 µm. Commercial plates with a preadsorbant zone can be used if they are specified in a monograph. Sample applied to the preabsorbant region develops into sharp, narrow bands at the preabsorbant-sorbent interface. Alternatively, flat *glass plates* of convenient size, typically 20 cm × 20 cm can be coated as described under *Preparation of Chromatographic Plates.*

A suitable *manual, semiautomatic, or automatic application device* can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a *template* can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates. For the proper application of the solutions, *micropipets, microsyringes,* or *calibrated disposable capillaries* are recommended.

For ascending development, a *chromatographic chamber* made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.

Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.

A *UV light source* suitable for observations under short (254 nm) and long (365 nm) wavelength UV light.

A suitable *device for documentation* of the visualized chromatographic result.

Procedure—Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter (1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm (5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge—during chromatography the application position must be 3 mm (HPTLC) to 5 mm (TLC) above the level of the developing solvent—and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm (5 mm on HPTLC plates) between the centers of spots or 4 mm (2 mm on HPTLC plates) between the edges of bands, and allow to dry.

Ascending Development—Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impregnation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromato-

graphic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.

Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Horizontal Development—Introduce a sufficient quantity of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.

For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection—Observe the dry plate first under short-wavelength UV light (254 nm) and then under long-wavelength UV light (365 nm) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the R_F values for the principal spots or zones (see *Glossary of Symbols*).

Quantitative Measurement—Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see *Radioactivity* ⟨821⟩).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the x-axis and the y-axis, a recorder, a suitable integrator or a computer; and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not fewer than three standard solutions of the substance to be examined, the concentrations of which span the expected

value in the test solution (e.g., 80%, 100%, and 120%). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

Preparation of Chromatographic Plates—

Apparatus—

Flat *glass plates* of convenient size, typically 20 cm × 20 cm.

An *aligning tray* or a flat surface upon which to align and rest the plates during the application of the adsorbent.

A *storage rack* to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The *adsorbent* consists of finely divided adsorbent materials, normally 5 to 40 µm in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris (calcium sulfate hemihydrate [at a ratio of 5% to 15%]) or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.

A *spreader,* which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate.■2S (*USP28*)

Procedure—[NOTE—In this procedure, use purified water that is obtained by distillation.] Clean the

■glass■2S (*USP28*)
plates scrupulously, ~~as by immersion in chromic acid cleansing mixture,~~

■using an appropriate cleaning solution (see *Cleaning Glass Apparatus* ⟨1051⟩),■2S (*USP28*)

rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a 5- × 20-cm plate adjacent to the front edge of the first square plate and another 5- × 20-cm plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five 20- × 20-cm plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at 105° for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.

~~Place two filter paper wicks, 18 cm in height and as wide as the length of the developing chamber, into the chamber, add about 100 mL of the solvent (sufficient to have a depth of 5 to 10 mm at the bottom of the chamber), seal the cover to the top of the chamber, and allow the system to equilibrate; it is essential that the wicks become completely wet. Alternatively, the chamber may be completely lined with filter paper. In either case, assure that the filter paper dips into the solvent at the bottom of the chamber. Where vapor saturation of the chamber by these methods is undesirable, it is so indicated in the individual monograph.~~

~~Apply the test solution and the standard solution, as directed in the individual monograph, at points about 1.5 cm apart and about 2 cm from the lower edge of the plate (the lower edge is the first part over which the spreader moved in the application of the adsorbent layer), and allow to dry. Avoid physical disturbance of the adsorbent during the spotting procedure (by the pipet or other applicator) or when handling the plates. The template will aid in determining the spot points and the 10- to 15-cm distance through which the solvent front should pass.~~

~~Place a mark 10 to 15 cm above the spot point. Arrange the plate on the supporting rack (test spots toward the bottom), and introduce the rack into the developing chamber. Allow the solvent in the chamber to reach the lower edge of the adsorbent, but do not allow the spot points to be immersed. Put the cover in place, and maintain the system until the solvent ascends to a point 10 to 15 cm above the initial spots, this usually requires about 15 minutes to 1 hour. Remove the plate from the developing chamber, mark the solvent front, air-dry the plates, and observe first under short-wavelength UV light (254 nm) and then under long-wavelength UV light (360 nm). Measure and record the distance of each spot from the point of origin, and indicate for each spot the wavelength under which it was observed. Determine the R_F values for the principal spots (see *Glossary of Symbols*). If further directed, spray the spots with the reagent specified, observe, and compare the test chromatogram with the standard chromatogram.~~

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~~Continuous Development Thin-Layer Chromatography~~

~~In contrast to conventional thin-layer chromatography, which is carried out in a closed tank, the continuous development or continuous flow technique allows the upper end of the plate to project through a slot in the cover of the developing chamber. When the developing solvent reaches the slot, continuous evaporation occurs, producing a steady flow of solvent over the plate. In conventional thin layer chromatography, spot migration ceases when the solvent reaches the top of the plate, after which the spots simply enlarge by diffusion. In the continuous flow process, spot migration continues as long as the plate remains in the tank and the developing solvent is not exhausted.~~

~~Development may be continued for several hours after the solvent reaches the top of the plate, to provide adequate migration of the spots. Usually spots of a standard solution, a test solution, and a mixture of equal amounts of test and standard solutions, are initially applied at a standard distance from the base of the plate. Identity of the standard and test substances is confirmed by their migrating equal distances from the origin and by the observation that the two substances applied as a mixture show no tendency to separate.~~

~~A major advantage of continuous development thin layer chromatography stems from the greater solvent selectivity for solvents of low solvent strength. Solvent strength refers to the property of a developing solvent that causes solutes to migrate, and it is strongly influenced by the polarity of the solvent. Increasing the solvent strength by adding a more polar solvent causes the R_F value to increase. Solvent selectivity refers to the ability of a solvent system to produce different R_F values for closely related substances. In conventional thin layer chromatography, a solvent system giving an R_F value in the range of 0.3 to 0.7, but with adequate selectivity to permit separation of the substances being examined is usually selected. It is much easier to find solvent systems producing adequate migration than to find those affording adequate selectivity.~~

~~Solvent systems of lower strength generally exhibit higher selectivity, but are difficult to employ in conventional thin layer chromatography because they result in very little migration before the solvent reaches the top of the plate. Migration may be increased, however, by repeated drying and redevelopment of the plate or, more conveniently, by providing means for evaporation of solvent at the top of the plate, which results in continuous development. Two techniques are used: continuous development and short bed continuous development thin layer chromatography.~~

~~An R_F value cannot be measured in continuous development thin layer chromatography. Substances may be compared either by their migration distance over a fixed period of time or by comparison with the migration of a standard substance applied to the plate.~~

~~CONTINUOUS DEVELOPMENT~~

~~**Apparatus**—Acceptable apparatus and materials for continuous development thin layer chromatography are the same as those described under conventional *Thin-Layer Chromatography,* except as follows.~~

~~A *developing chamber* is used that consists of a rectangular tank, approximately 23 cm × 23 cm × 9 cm, equipped with a glass solvent trough and a platform about 3.75 cm high to elevate the solvent trough above the base of the tank. The chamber is fitted with a cover having a 21 × 6 cm slot in the front edge.~~

~~**Procedure**—Apply the standard solution, the test solution, and a mixture of equal amounts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the elevated empty solvent trough with the adsorbent on the underside of the leaning plate. The adsorbent rests against a piece of heavy (about 1 mm thick)[2] filter paper measuring 20 cm × 3 cm, folded lengthwise and placed over the front edge of the tank. Place the developing solvent in the trough; set the cover in place, and seal all openings except where the adsorbent contacts the paper wick. The plate extends about 1 cm beyond the top of the tank. After the solvent reaches the top of the plate, allow development to continue for an appropriate time. Then remove and dry the plate, and detect the spots by suitable means.~~

~~SHORT-BED CONTINUOUS DEVELOPMENT~~

~~A major advantage of the short bed technique derives from the fact that solvent velocity is inversely related to bed length. Since spot migration depends upon the total amount of solvent passing over the plate, the short bed permits useful migration to be obtained in a reasonable time with solvent having very low solvent strength. Lower diffusion in solvents of low solvent strength produces smaller and more dense spots, which enhances both detectability and discernment of small differences in migration distance.~~

~~**Apparatus**—Acceptable apparatus and materials for short bed continuous development thin layer chromatography are the same as those described under conventional *Thin-Layer Chromatography*, except as follows.~~

~~A shallow *developing chamber*[3] approximately 22 cm × 9 cm × 3 cm, equipped with a cover plate and tight fitting polytef wings that enable the chamber to be sealed against the plate, is used. The inside bottom of the chamber contains ridges that support the plate and allow it to be inserted at different angles, thereby varying the length of the plate contained within the tank.~~

~~**Procedure**—Apply the standard solution, the test solution, and a mixture of equal parts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the developing chamber (adsorbent side up), and add the developing solvent to the chamber. No paper wick is employed. After the solvent reaches the top of the plate, allow development to continue for an appropriate time. Then remove and dry the plate, and detect the spots by suitable means.~~

■■2S (*USP28*)

Change to read:

INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2, where t_1 and t_2 are the respective retention times; and h, $h/2$, and $W_{h/2}$ are the height, the half-height, and the width at half-height, respectively, for peak 1. W_1 and W_2 are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.

[2] ~~Whatman No. 3MM filter paper or equivalent.~~

[3] ~~Suitable equipment is available from Regis Chemical Company, Morton Grove, IL.~~

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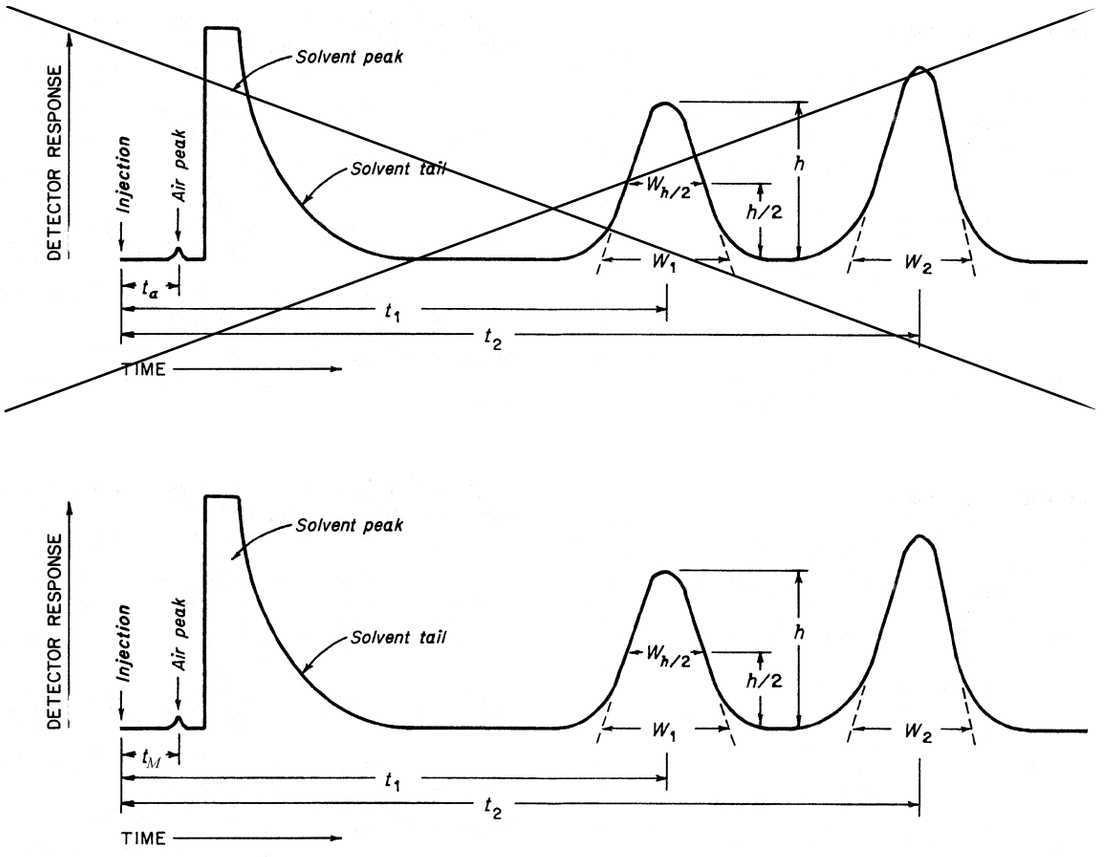

Fig. 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next. ~~Comparisons are normally made in terms of relative retention, α, r, which is calculated by the equation:~~

~~$$\alpha = \frac{t_2 - t_a}{t_1 - t_a},$$~~

~~$$r = \frac{t_2 - t_a}{t_1 - t_a}$$~~

~~where t_a and t_a are the retention times, measured from the point of injection, of the test and reference substances, respectively, determined under identical experimental conditions on the same column, and t_a is the retention time of a nonretained substance, such as methane in the case of gas chromatography.~~

~~In this and the following expressions, the corresponding retention volumes or linear separations on the chromatogram, both of which are directly proportional to retention time, may be substituted in the equations. Where the value of t_a is small, R_a or R_a may be estimated from the retention times measured from the point of injection (t_2/t_1).~~

~~R_a~~

▲Due to the fact that most procedures do not need to identify an unretained peak, comparisons are normally made in terms of relative retention times R_r:

$$R_r = \frac{t_2}{t_1},$$

where t_2 and t_1 are the retention times, measured from the point of injection, of the test and the reference substances, respectively, determined under indentical experimental conditions on the same column.

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Other procedures may identify the peak position using the relative retention *r*:

$$r = \frac{t_2 - t_M}{t_1 - t_M},$$

where t_M is the retention time of a non-retained marker, which needs to be defined in the procedure.▲*USP29*

The number of theoretical plates, *N,* is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:

~~$N = 16\left(\frac{t}{W}\right)^2$ or $N = 5.54\left(\frac{t}{W_{h/2}}\right)^2$,~~

▲$N = 16\left(\frac{t}{W}\right)^2$, ▲*USP29*

where *t* is the retention time of the substance and *W* is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. ~~$W_{h/2}$ is the peak width at half-height, obtained directly by electronic integrators.~~

▲▲*USP29*

The value of *N* depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, *R,* is determined by the equation:

$$R = \frac{2(t_2 - t_1)}{W_2 + W_1},$$

in which t_2 and t_1 are the retention times of the two components, and W_2 and W_1 are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, *R,* by the equation:

$$R = \frac{2(t_2 - t_1)}{1.70(W_{1,h/2} + W_{2,h/2})},$$

and to determine the number of theoretical plates, *N,* by the equation:

$$N = 5.54(t/W_{h/2})^2,$$

▲where $W_{h/2}$ is the peak width at half-height, obtained directly by electronic integrators.▲*USP29*

However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, 0.5% impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

Change to read:

SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the

■detection sensitivity,■1S *(USP29)*

resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The 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.

■The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the *Chromatographic purity* or *Related compounds* tests by injecting a volume of a quantitation limit solution equal to that of the *Test so-*

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lution. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the *Test solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test solution* in the case of drug substances, and at a 0.1% level relative to the amount of drug substance in the *Test solution* for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.■1S (*USP29*)

The resolution, *R,* [NOTE—All terms and symbols are defined in the *Glossary of Symbols*] is a function of the column efficiency, *N,* and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, S_R, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.

The tailing factor, *T,* a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see *Figure 2*). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.

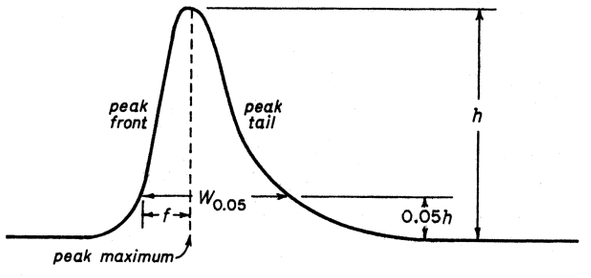

Fig. 2. Asymmetrical chromatographic peak

These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see *Procedures* under *Tests and Assays* in the *General Notices*). ~~Adjustments of operating conditions to meet system suitability requirements may be necessary.~~

■If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum ~~specification~~ variation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when ~~Reference Standards~~ suitable standards (including Reference Standards) are available for all ~~analytes~~ compounds used in the suitability test and only when those standards are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. ~~The changes described below may require additional validation data unless the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.~~ The changes described below may require additional validation data. The user should verify the suitability of the method under the new conditions by assessing the relevant analytical performance characteristics potentially affected by the change. *Tables 1* and *2* in the general information chapter *Verification of Compendial Procedures* ⟨1226⟩ provide lists of analytical performance validation characteristics that may require assessment. Multiple adjustments can have a cumulative effect in the performance of the system and should be considered carefully before implementation.

pH of Mobile Phase (HPLC)—The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within ~~0.2~~ ±0.2 units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within ±10%, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC)— ~~The amount of the minor~~ The following adjustment limits apply to minor components of the mobile phase (specified at 50% or less). The amount(s) of these component(s) can be adjusted by ±30% relative. ~~or ±2% absolute (i.e., in relation to the total mobile phase), whichever is larger.~~ However, the change in any component cannot exceed ±10% absolute (i.e., in relation to the total mobile phase), nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

Binary Mixtures—

SPECIFIED RATIO OF 50 : 50—Thirty percent of 50 is 15% absolute, but this exceeds the maximum permitted change of ±10% absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40 : 60 to 60 : 40.

~~SPECIFIED RATIO OF 95 : 5 Thirty percent of 5 is 1.5% absolute. However, because adjustments up to ±2% absolute are allowed, the ratio may be adjusted within the range of 93 : 7 to 97 : 3.~~

SPECIFIED RATIO OF 2 : 98—Thirty percent of 2 is 0.6% absolute. ~~In this case an absolute adjustment of ±2% is not allowed because it would reduce the amount of the first component to zero.~~ Therefore the maximum allowed adjustment is within the range of 1.4 : 98.6 to 2.6 : 97.4.

Ternary Mixtures—

SPECIFIED RATIO OF 60 : 35 : 5—For the second component, 30% of 35 is 10.5% absolute, which exceeds the maximum permitted change of ±10% absolute in any component. Therefore the second component may be adjusted only within the range of 25% to 45% absolute. For the third component, 30% of 5 is 1.5% absolute. ~~Since ±2% absolute is permitted and provides more flexibility, the third component may be adjusted within the range of 3% to 7% absolute.~~ In all cases, a sufficient quantity of the first component is used to give a total of 100%. Therefore, mixture ranges of 50 : 45 : 5 to 70 : 25 : 5 or ~~58 : 35 : 7 to 62 : 35 : 3~~ 58.5 : 35 : 6.5 to 61.5 : 35 : 3.5 would meet the requirement.

~~Detector~~ Wavelength of UV-Visible Detector (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, ±3 nm.

Column Length (GC, HPLC): can be adjusted by as much as ~~70%.~~ ±70%.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as ~~±25% 50%.~~ ±25% for HPLC and ±50% for GC.

Film Thickness (Capillary GC): can be adjusted by as much as –50% to 100%.

Particle Size (HPLC): can be reduced by as much as 50%.

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Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as ±50%.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. ~~It may be increased to as much as twice the volume specified, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity, and retention times.~~

Column Temperature (HPLC): can be adjusted by as much as ~~±20°.~~ ±10°. Column thermostating is recommended to improve control and reproducibility of retention time.

~~**Column** **Oven Temperature (GC):** can be adjusted by as much as ±2%, in terms of absolute temperature.~~ ±10%.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to ±20% is permitted.

~~**Gradient Elution (HPLC)** The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column.~~ ■1S (*USP29*)

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

■Relative retention times may be provided in monographs for informational purposes only, to aid in peak identification. There are no acceptance criteria applied to relative retention times.■1S (*USP29*)

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.

The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails

■system suitability■1S (*USP29*) requirements are unacceptable.

Change to read:

GLOSSARY OF SYMBOLS

To promote uniformity of interpretation, the following symbols and definitions are employed where applicable in presenting formulas in the individual monographs.

▲Where a different symbol or definition is used in an individual monograph, the monograph text takes precedence (see *General Notices*).▲*USP29*

[NOTE—Where the terms W and t both appear in the same equation they must be expressed in the same units.]

~~α~~ ~~relative retention,~~

~~$\alpha = \frac{t_2 - t_a}{t_1 - t_a}$.~~

~~e_a, e_s, e_u~~ ~~concentrations of Reference Standard, internal standard, and analyte in a particular solution.~~

~~C_u~~ ~~concentration ratio of analyte and internal standard in test solution or *Assay preparation*,~~

~~$C_A = \frac{C_u}{C_i}$.~~

~~C_s~~ ~~concentration ratio of Reference Standard and internal standard in Standard solution,~~

~~$C_S = \frac{c_i}{c_s}$.~~

▲▲*USP29*

f distance from the peak maximum to the leading edge of the peak, the distance being measured at a point 5% of the peak height from the baseline.

k' capacity factor,

$$k' = \frac{\text{amount of substance in stationary phase}}{\text{amount of substance in mobile phase}}$$

~~$k' = \frac{\text{time spent by substance in stationary phase}}{\text{time spent by substance in mobile phase}} = \frac{t}{t_a} - 1.$~~

▲$k' = \frac{\text{time spent by substance in stationary phase}}{\text{time spent by substance in mobile phase}} = \frac{t}{t_M} - 1.$ ▲*USP29*

N number of theoretical plates in a chromatographic column,

~~$N = 16\left(\frac{t}{W}\right)^2.$~~

▲$N = 16\left(\frac{t}{W}\right)^2$ or $N = 5.54\left(\frac{t}{W_{h/2}}\right)^2$. ▲*USP29*

~~q_u, q_r, q_s~~ ~~total quantities (weights) of Reference Standard, internal standard, and analyte in a particular solution.~~

~~Q_u~~ ~~quantity ratio of analyte and internal standard in test solution or *Assay preparation*,~~

~~$Q_A = \frac{q_u}{q_r}.$~~

~~Q_s~~ ~~quantity ratio of Reference Standard and internal standard in Standard solution,~~

~~$Q_S = \frac{q_s}{q_r}.$~~

▲r relative retention,

~~$r = \frac{t_2 - t_a}{t_1 - t_a}$~~

$$r = \frac{t_2 - t_M}{t_1 - t_M},$$

r_i peak response of an impurity obtained from a chromatogram.

~~r_s~~, r_{IS} peak response of the internal standard obtained from a chromatogram. ▲*USP29*

r_S peak response of the Reference Standard obtained from a chromatogram.

r_U peak response of the analyte obtained from a chromatogram.

R resolution between two chromatographic peaks,

$$R = \frac{2(t_2 - t_1)}{W_1 + W_2}.$$

▲or $R = \frac{2(t_2 - t_1)}{1.70(W_{1,h/2} + W_{2,h/2})}$ ▲*USP29*

R_F chromatographic retardation factor equal to the ratio of the distance from the origin to the center of a zone divided by the distance from the origin to the solvent front.

~~R_s~~ ~~relative retention~~

~~$R_r = \frac{\text{distance traveled by test substance}}{\text{distance traveled by standard}}.$~~

▲~~R_s~~ ▲*USP29* relative retention time

▲R_r ▲*USP29*

~~$R_R = \frac{t_2}{t_1}$~~

$$R_r = \frac{t_2}{t_1}$$

R_{rel} ▲ relative retardation

$$R_{rel} = \frac{\text{distance traveled by test substance}}{\text{distance traveled by standard}}$$ ▲*USP29*

R_S peak response ratio for a Standard preparation containing Reference Standard and internal standard,

~~$R_S = \frac{r_s}{r_1}$~~

$$R_S = \frac{r_s}{r_{IS}}$$ ▲*USP29*

R_U peak response ratio for *Assay preparation* containing the analyte and internal standard,

~~$R_U = \frac{r_U}{r_1}$~~

$$R_U = \frac{r_U}{r_{IS}}$$ ▲*USP29*

S_R (%) relative standard deviation in percentage,

$$S_R\,(\%) = \frac{100}{\bar{X}}\left[\frac{\sum_{i=1}^{N}(X_i - \bar{X})^2}{N-1}\right]^{1/2},$$

where X_i is an individual measurement in a set of N measurements and X is the arithmetic mean of the set.

T tailing factor,

$$T = \frac{W_{0.05}}{2f}.$$

t retention time measured from time of injection to time of elution of peak maximum.

t_a retention time of nonretarded component, air with thermal conductivity detection.

W width of peak measured by extrapolating the relatively straight sides to the baseline.

$W_{h/2}$ width of peak at half height.

$W_{0.05}$ width of peak at 5% height.

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,

■or a monolithic silica rod.■1S (*USP29*)

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, ■3 to■1S (*USP28*) 10 µm in diameter.

L9—~~10 µm~~

■■1S (*USP29*)

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Irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating,

■3 to 10 µm in diameter.■1S (*USP29*)

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 ■■1S (*USP28*) having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating, ■5 to 10 µm in diameter.■1S (*USP28*)

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]

■[NOTE—Available as YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. and distributed by Waters Corp. (www.waters.com).]■1S (*USP29*)

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~~

■3■1S (*USP29*)
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 ■hydroxide-selective,■1S (*USP29*) 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 by molecular size over a range of 4000 to 500,000 Da. It is spherical, silica-based, and processed to provide pH stability.[6]

■[NOTE—Available as TSKgel G4000 SWXL from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

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, 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,■about■1S (*USP28*) 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.[7]

■[NOTE—Available as CarboPac MA1 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

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 YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■ and distributed by Waters Corp. (www.waters.com).■1S (*USP29*)~~

[6] ~~Available as TSKgel G4000 SWXL from ■Tosoh Biosep (www.tosohbiosep.com).■1S (*USP29*)~~

[7] ~~Available as CarboPac MA1 and distributed by Dionex ■Corp. (www.dionex.com).■1S (*USP29*)~~

[8] ~~Available as Zirchrom-PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.~~

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■[NOTE—Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.]■1S *(USP29)*

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]

■[NOTE—Available as OmniPac PAX-500 and distributed by Dionex Corp. (www.dionex.com).]■1S *(USP29)*

L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.[10]

■[NOTE—Available as Chiralpak AD from Chiral Technologies, Inc., ■(www.chiraltech.com).■1S *(USP28)*]■1S *(USP29)*

L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.[11]

■[NOTE—Available as TSK IC SW Cation from Tosoh Biosep (www.tosohbiosep.com).]■1S *(USP29)*

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]

■[NOTE—Available as IonPac CS14 distributed by Dionex Corp. (www.dionex.com).]■1S *(USP29)*

L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter. [13]

■[NOTE—Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).]■1S *(USP29)*

L55—A strong cation-exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.[14]

■[NOTE—Available as IC-Pak C M/D from Waters Corp. (www.waters.com).]■1S *(USP29)*

L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.[15]

■[NOTE—Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem).]■1S *(USP29)*

L57—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å.

■[NOTE—Available as Ultron ES-OVM from Agilent Technologies (www.agilent.com/chem).]■1S *(USP29)*

L58—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.[16]

■[NOTE—Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) www.bio-rad.com.]■1S *(USP29)*

L59—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.[17]

■[NOTE—Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively) (www.tosohbiosep.com).]■1S *(USP29)*

L60—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]~~.~~[18]

■[NOTE—Available as Supelcosil ABZ from Supelco (www.sigma-aldrich.com/supelco).]

L61—A hydroxide-selective, strong anion-exchange resin consisting of a highly cross-linked core of 13 µm microporous particles having a pore size less than 10 Angstrom units and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene with a latex coating composed of 85 nm diameter microbeads bonded with alkanol quartenary ammonium ions (6%).

[NOTE—Available as Ion Pac AS-11 and AG-11 from Dionex (www.dionex.com).]■1S *(USP29)*

~~[9] Available as OmniPac PAX-500 and distributed by Dionex ■Corp. (www.dionex.com).■1S *(USP28)*~~

~~[10] Available as Chiralpak AD from Chiral Technologies, Inc., ■(www.chiraltech.com).■1S *(USP28)*~~

~~[11] Available as TSK IC SW Cation from ■Tosoh Biosep (www.tosohbiosep.com).■1S *(USP28)*~~

~~[12] Available as IonPac CS14 distributed by Dionex ■Corp.■1S *(USP28)* (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).~~

~~[16] Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) (www.bio-rad.com).~~

~~[17] Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively). (www.tosohbiosep.com).~~

~~[18] Available as Supelcosil ABZ from Supelco. (www.sigma-aldrich.com/supelco).~~

■~~L61~~ ## (Lycopene, Lycopene Preparation, YMC 30)—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter.■2S (*USP28*)

~~L## (Enoxaparin Sodium Injection, IonPac AG11)—[To come.]~~

~~L## (Enoxaparin Sodium Injection, IonPac AS11)—[To come.]~~

~~L## (Enoxaparin Sodium, Dowex 1X8)—[To come.]~~

~~L## (Enoxaparin Sodium, Dowex 50WX2)—[To come.]~~

■L## (Dalteparin Sodium, anion-exchange Dowex 1X8)—[To come.]

L## (Dalteparin Sodium, cation-exchange Dowex 50WX2)—[To come.]■2S (*USP28*)

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.~~

■[NOTE—Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.]■1S (*USP29*)

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.[19]

■[NOTE—A suitable grade is available commercially as ''SP2100/0.1% Carbowax 1500'' from Supelco, Inc. (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

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.[20]~~

■■1S (*USP29*)

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[21]

■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)
to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed.[21]

~~[19] A suitable grade is available commercially as ''SP2100/0.1% Carbowax 1500'' from Supelco, Inc., ■(www.sigma-aldrich.com/supelco).■1S (*USP28*)~~

~~[20] A suitable grade is available commercially as ''Optima Delta-3'' from Machery-Nagel, Inc., 215 River Vale Road, River Vale, NJ 07675.~~

~~[21] Unless otherwise specified in the individual monograph, silanized support is intended.~~

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■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)

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.[22]

■[NOTE—Commercially available as SP1500 on Carbopack B from Supelco (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

BRIEFING

⟨**644**⟩ **Conductivity.** It is proposed to add this new general chapter to address a need based upon proposed revisions of the packaged water monographs, which appear elsewhere in this issue of *PF*. The conductivity limits in these monographs are harmonized with the *European Pharmacopoeia,* and the conductivity test procedure is provided by reference to EP section 2.2.38. It therefore became necessary for the Committee to develop a new general chapter in which the content is a very loose adaptation of that EP section. This chapter provides information that can be used for testing conductivity when appropriate for any article, whereas the general chapter *Water Conductivity* ⟨645⟩ is restricted to water testing. Comments should be addressed to Frank Barletta, liaison to the Pharmaceutical Waters Expert Committee.

(PW: F. Barletta) RTS—42230-1

[22] ~~Commercially available as SP1500 on Carbopack B from Supelco (www.sigma-aldrich.com/supelco).~~

Add the following:

■⟨644⟩ CONDUCTIVITY

INTRODUCTION

Conductivity is the measurement of the ability of a fluid to conduct electricity via the ions in that fluid. The measurement is non-ion-specific, and all ions respond with different equivalent conductances, λ. Despite the lack of specificity, conductivity is a valuable overall tool for measurement and control of total ionic content because it is directly proportional to the concentration of each ionic species, C_i, as described in the equation below.[1] Conductivity, κ, defined in the equation below, is measured using an alternating current in order to prevent (1) polarization (or collection of ions) at the electrodes or (2) any electrolytic reaction.

$$\kappa = 1000 \sum_{i}^{\substack{all \\ ions}} C_i \lambda_i$$

The technique is valid for use with all concentrations of ionic species ranging from acids and bases (high conductivity) to pure water (low conductivity) and even to organic, nonionic species such as glycols. The measurement can be sensitive to ion concentrations as low as 0.05 ppb.

[1] At low ion concentrations, the conductivity–concentration relationship is valid. As ion concentrations increase ($> 10^{-3}$ mol/L), small negative deviations from linearity arise as a result of decreases in λ for each ion. Those deviations vary from ion to ion. For some acids and bases, the extent of dissociation into ions also may decrease as a result of molecular interactions, thereby lowering the solution conductivity. At some concentrations of strong acids, usually >10% to 15%, the negative deviations persist, and in some cases, the conductivity may decrease with increasing concentration.

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The conductivity of fluids in pharmaceutical systems varies greatly. The quantity of ions present in *Purified Water* or *Water for Injection* is very low, resulting in a conductivity of <5 µS/cm and often in a conductivity approaching <0.055 µS/cm. In drinking waters, the conductivity may vary from 30 to 1000 µS/cm. In chromatographic separations, the conductivity of the eluent may vary from 100 to 100,000 µS/cm. For hot concentrated acids, the conductivity may be as much as 1,000,000 µS/cm.

The conductivity of a solution (κ, in siemens/cm) is related to the conductance, K(siemens), between two electrodes according to the following equation:

$$\kappa = K \times \left[\frac{d}{A}\right] = K \times \theta,$$

in which A is the area of the conducting electrodes (cm^2) and d is the distance between the electrodes (cm). Although S/m is the appropriate SI unit for conductivity, historically units of S/cm have been selected as the accepted unit for conductivity. The reciprocal of conductivity is resistivity, ρ, (ohm-cm), and is given by the following equation:

$$\rho = \frac{1}{\kappa} = \frac{1}{K \times \theta} = \frac{R}{\theta},$$

in which R is the resistance of the fluid between the electrodes [ohm (Ω) = 1/siemens (S)]. The geometrical ratio, d/A (or θ), is known as the cell constant (cm^{-1}) of the sensor. Because the conductance of a fluid is proportional to the area of the electrodes and inversely proportional to the distance between the electrodes, the conductance is normalized for the geometrical construction of the two electrodes, resulting in the conductivity. It is the conductivity that is proportional to the ionic content of the fluid. Similarly, it is the resistivity that is inversely proportional to the ionic content of the fluid.

There is no difference in the physical measurement of conductivity and resistivity. They are reciprocals of each other (see units above). Therefore, if one measurement is known, then the other value is readily calculated by taking the reciprocal of the numerical value and the units. There is no difference in the instrumentation or the sensors. The only difference is in how the measured value is reported or displayed for the convenience of the analyst. For example, 1 MΩ-cm = 1 µS/cm and 5 kΩ-cm = 0.2 mS/cm.

Cell Constant Determination—The distinction between resistivity (or conductivity) and the more common electrical term resistance (or conductance) can be confusing. When two electrodes are placed in a conducting fluid and a voltage is applied to them, there is a resistance between the electrodes. If the electrodes are placed farther apart, the resistance increases (or conductance decreases). If the area of the electrodes increases, then the resistance decreases (or conductance increases). In both cases, the ionic concentration does not change, but the geometrical factor affects the

resistance. The purpose of the cell constant is to normalize the resistance measurement for the geometrical construction of the two electrodes, resulting in the resistivity (or conductivity). The cell constant (θ) is defined as the distance (d) between the electrodes divided by the area (A) of the electrodes according to the following equation:

$$\theta(\mathrm{cm}^{-1}) = \frac{d(\mathrm{cm})}{A(\mathrm{cm}^2)}.$$

For sensors of modern construction, the exact measurement of the cell constant obtained by directly measuring d and A is impractical because of the various geometrical configurations and the nonuniformity of the electric field between the electrodes. The cell constant is usually determined by immersing the conductivity sensor in a solution of known conductivity. Typically, the conductivity analyzer computes the cell constant by measuring the conductance of a solution of known conductivity, and entering the known conductivity into the meter. The analyzer then solves for θ.

Solutions of known conductivity, traceable to authoritative agencies, are not as common as other solutions such as pH buffers or other reference solutions. Examples of some competent authorities include, but are not limited to, ASTM and NIST. ASTM D1125, *Standard Test Method for Electrical Conductivity and Resistivity of Water,* is an established method that provides the procedure for preparing solutions of known conductivity ranging from ~150 to 100,000 µS/cm. NIST and other national agencies offer various reference conductivity solutions over a similar range. Water with no impurities or exposure to air (also known as ultrapure water) is a reliable reference conductivity material below 10 µS/cm because the fundamental conductivity of pure water is known precisely as a function of temperature.

Temperature Compensation—Temperature compensation is usually a requirement for most conductivity measurements, though there are exceptions such as those discussed in *Water Conductivity* ⟨645⟩. The conductivity of a fluid is related to the temperature. As the temperature increases, ions are more mobile and the conductivity increases. The effect of temperature depends on the type and concentration of the ion, but for most solutions with conductivities >10 µS/cm, the impact of temperature is in the range of 1.9% to 2.2% of the reading per degree. For strong acids, this may be as low as 1.5% per degree. For high-purity water, the temperature coefficient could vary anywhere from 2.0% to 7.5% per degree, depending on the temperature and purity of the water. For each case described here, some knowledge of the type of impurity is needed in order to ensure adequate temperature compensation. If the temperature coefficient is constant and linear, the equation that relates the compensated conductivity to the non-temperature compensated conductivity is the following:

$$\kappa_{25} = \frac{\kappa_t}{[1+\alpha(t-25)]},$$

in which t is the measured temperature, κ_{25} is the conductivity compensated to 25°, κ_t is the conductivity at t, and α is 0.02 for a temperature coefficient of 2% per degree.

Most conductivity analyzers directly measure the uncompensated conductivity and the temperature, and the temperature-compensated conductivity is determined via mathematical algorithms in the microprocessor of the analyzer. Depending on the application and knowledge of the content of the fluid, different compensation algorithms may be available. For many process control applications, temperature compensation is usually advisable. When the uncompensated conductivity changes, it is impractical to

distinguish whether this change is due to a change in temperature or a change in ionic content. Temperature compensation allows the analyst to distinguish between changes in temperature or ionic content. Compensation to a reference temperature of 25° is standard practice.

CALIBRATION

Although specific details will vary, the conductivity measurement system is calibrated in three stages: first, the analyzer electronic circuitry; second, the temperature sensor; and third, the cell constant of the conductivity sensor. Depending on the type of sensor and analyzer, calibration cycles will vary widely from weekly to annually depending on manufacturer's recommendations and application requirements.

Instrument Calibration—Calibrate the analyzer electronic circuitry by disconnecting the sensor and connecting precision resistors (resistors of known value) to the analyzer. The resistors shall be traceable to a competent national authority. The resistance values shall be selected such that (1) they are in the range of measurement capability of the analyzer, and (2) they are in the range of the conductivity to be measured. Because the analyzer may have multiple circuits internally, verification of the appropriate circuit and measurement range is necessary. Comparison of the measured resistance with the actual resistance will verify whether the analyzer is properly calibrated. The resulting difference shall be within 2% of the actual resistance. Adjustment of the resistance measurement circuit is necessary if this limit is exceeded.

If a temperature measurement circuit is integrated into the analyzer and utilized as part of the measurement system, then verification of this circuit is required. Depending on the type of temperature device located at the sensor (this could be an RTD, thermistor, or thermocouple), an appropriate signal source (resistor, voltage, etc.) should be input to the analyzer. Comparison of the measured temperature with the simulated temperature will verify whether the temperature measurement circuit is properly calibrated. The resulting difference shall be within 0.5° of the simulated temperature. Adjustment of the temperature measurement circuit is necessary if this limit is exceeded.

Temperature Sensor Calibration—If a temperature sensor is integrated into the conductivity sensor, the temperature sensor shall have an accuracy of ±2° compared to a reference system. The reference system can be another traceable temperature measurement device, or it can be a system of known temperature such as boiling water (corrected for elevation, if necessary) or an ice-water bath. Adjustment of the temperature sensor calibration is recommended if the 1° accuracy is exceeded.

Cell Constant Calibration—The cell constant of the sensor is calibrated by placing the sensor in a solution of known conductivity traceable to the competent authority, as described above. Adjustment of the cell constant calibration is recommended if the difference between the actual and measured conductivity exceeds 2% of the actual conductivity. Specific reference solutions are not listed here because various options exist as described above.

Because the cell constant is a geometrical property of the sensor, and it is a constant, the determination of the cell constant does not need to be in the range of operation of the pharmaceutical process. However, the cell constant calibration should be done with a solution that is in the operational range of the analyzer. In addition, cell constant calibration should be performed in the recommended temperature range of the reference solution. Cell constant calibration can be performed with or without temperature compensation depending on the reference solution. For reference solutions

exceeding 10 µS/cm, if temperature compensation is needed, a temperature coefficient (α) of 2% per degree is sufficient over the range of $25 \pm 10^{\circ}$ unless otherwise specified.

METHOD

Determination of the Conductivity of the Solution To Be Examined—If the conductivity measurement is not a continuous process measurement, but is based on a grab sample, the sensor should be carefully handled and cleaned. The sensor should be rinsed with a suitable quality of water, and then rinsed at least 1 to 2 times with the solution to be measured. The procedure may vary depending on the solution to be tested. For very low conductivity samples such as pharmaceutical grade water, more rinsing may be needed to remove any remaining residue from the sensor. Similarly, the sample should be transferred to a container that has been cleaned using a method similar to that used for the sensor. Transfer an appropriate volume of fluid to the container, and immerse the sensor. If a temperature-compensated measurement is advised, then select the appropriate temperature compensation algorithm, and adjust the sample temperature to the recommended range, if necessary. Otherwise, disable the temperature compensation. Verify that the temperature is sufficiently stable ($< 0.25^{\circ}$), and record the conductivity reading and the temperature, if necessary.

If the conductivity sensor is immersed in a closed process, such as a piping system or tank, the sensor does not need to be removed and cleaned prior to measurement, except as required as part of the cleaning process for the entire system. If a temperature-compensated measurement is advised, then select the appropriate temperature compensation algorithm. Otherwise, disable the temperature compensation. Although temperature stability is desirable, it may not be possible depending on the process that is being measured. Record the conductivity reading and the temperature, if necessary.

This method can be implemented as an in-process online measurement as well as a laboratory measurement.■1S (*USP29*)

BRIEFING

⟨**785**⟩ **Osmolality and Osmolarity,** *USP 28* page 2444 and page 1702 of *PF* 30(5) [Sept.–Oct. 2004]. It is proposed to correct the molecular weight of vancomycin in the section on *Osmolarity.* Also, in the *Test Solution* under *Measurement of Osmolality,* because instructions to use a dilution factor in calculations may exist in specific cases, it is proposed to add a phrase to indicate that a dilution factor may be noted in a particular monograph. To address those instruments that are not designed to accept two calibration points in addition to water, changes in the *Procedure* are introduced along with acceptance criteria for calibration. An alternative procedure for calculations is also proposed.

(PA4: H. Pappa) RTS—41922-1; 41821-1

Change to read:

OSMOLARITY

Osmolarity of a solution is a theoretical quantity expressed in osmoles per L (Osmol per L) 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 = 328 mOsmol/L.~~

■[3 × 10 g/L/1485.71 (mol. wt. of vancomycin) + 2 × 9 g/L/58.5 (mol. wt. of sodium chloride)] × 1000 = 328 mOsmol/L.■1S (*USP29*)

The results suggest that the solution is slightly hyperosmotic since the osmolality of blood ranges between 285 and 310 mOsmol per kg. However, the solution is found to be hypo-osmotic and has an experimentally determined osmolality of 255 mOsmol per kg.[1] The example illustrates that osmolarity values calculated theoret-

[1] Kastango, E.S. and Hadaway, L. *International Journal of Pharmaceutical Compounding 5,* (2001) 465-469.

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ically 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 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.

Change to read:

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.

■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.■2S (*USP28*)

Standard Solutions—Prepare *Standard Solutions* as specified in *Table 1,* as necessary.

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,

■unless otherwise indicated in the monograph.■1S (*USP29*) 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.*

■[NOTE—If the instrument does not calibrate with multiple standards, calibrate the instrument by the manufacturer's instructions and confirm the instrument calibration with 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*. The instrument reading should be within ±2 mOsmol/kg from the *Standard Solution* (over the standard range of 100 to 700 mOsmol/kg).]■1S (*USP29*)

Table 1. Standard Solutions for Osmometer Calibration[2]

Standard Solutions (Weight in g of sodium chloride per kg of water)	Osmolality (mOsmol/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.

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.

■It can be shown from the above equation correlating osmolarity with osmolality that,

$$\xi_c = \xi_m (\rho - c),$$

where ρ is the density of the solution, and c is the total solute concentration, both expressed in g per mL. Thus, alternatively, the osmolarity can also be calculated from experimentally determined osmolality from the measurement of density of the solution by a suitable method and the total weight of the solute, after correction for water content, dissolved per mL of the solution.■1S *(USP29)*

GENERAL CHAPTERS

General Information

BRIEFING

⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding, *USP 28* page 2712. In the section *Application of Mean Kinetic Temperature,* it is proposed to add a sample calculation of the mean kinetic temperature (MKT) for the controlled cold temperature range in consideration of conditions during the storage, shipping, and distribution of pharmaceutical articles. (See *General Notices* for the definition of *Controlled Cold Temperature.*) In addition, editorial changes have been made to improve the readability of this chapter.

(PSD: C. Okeke) RTS—42362-1

Change to read:

BASIC PHARMACEUTICAL CALCULATIONS

The remainder of this chapter will focus on basic pharmaceutical calculations. It is important to recognize the rules involved when adding, subtracting, dividing, and multiplying values. The interrelationships between various units within the different weighing and measuring systems are also important and have to be understood.

Calculations in Compounding

The pharmacist must be able to calculate the amount or concentration of drug substances in each unit or dosage portion of a compounded preparation at the time it is dispensed. Pharmacists must perform calculations and measurements to obtain, theoretically, 100% of the amount of each ingredient in compounded formulations. Calculations must account for the active ingredient, or active moiety, and water content of drug substances, which includes that in the chemical formulas of hydrates. Official drug substances and added substances must meet the requirements under *Loss on Drying* ⟨731⟩, which must be included in the calculations of amounts and concentrations of ingredients. The pharmacist should consider the effect of ambient humidity on the gain or loss of water from drugs and added substances in containers subjected to intermittent opening over prolonged storage. Each container should be opened for the shortest duration necessary and then closed tightly immediately after use.

The nature of the drug substance that is to be weighed and used in compounding a prescription must be known exactly. If the substance is a hydrate, its anhydrous equivalent weight may need to be calculated. On the other hand, if there is adsorbed moisture present that is either specified on a certificate of analysis or that is determined in the pharmacy immediately before the drug substance is

used by the procedure under *Loss on Drying* ⟨731⟩, this information must be used when calculating the amount of drug substance that is to be weighed in order to determine the exact amount of anhydrous drug substance required.

There are cases in which the required amount of a dose is specified in terms of a cation [e.g., Li^+, netilmicin (n+)], an anion [e.g., F^-], or a molecule (e.g., theophylline in aminophylline). In these instances, the drug substance weighed is a salt or complex, a portion of which represents the pharmacologically active moiety. Thus, the exact amount of such substances weighed must be calculated on the basis of the required quantity of the pharmacological moiety.

The following formula may be used to calculate the exact theoretical weight of an ingredient in a compounded preparation:

$$W = ab/de,$$

in which W is the actual weighed amount; a is the prescribed or pharmacist-determined weight of the active or functional moiety of drug or added substance; b is the chemical formula weight of the ingredient, including waters of hydration for hydrous ingredients; d is the fraction of dry weight when the percent by weight of adsorbed moisture content is known from the loss on drying procedure (see *Loss on Drying* ⟨731⟩); and e is the formula weight of the active or functional moiety of a drug or added substance that is provided in the formula weight of the weighed ingredient.

EXAMPLE 1: Triturate Morphine Sulfate USP and Lactose NF to obtain 10 g in which there are 30 mg of Morphine Sulfate USP for each 200 mg of the morphine-lactose mixture. [NOTE—Clinical dosages of morphine mean Morphine Sulfate USP, which is the pentahydrate.]

Equation Factor	Numerical Value
W	weight, in g, of Morphine Sulfate USP
a	1.5 g of morphine sulfate pentahydrate in the prescription
b	759 g/mole
d	1.0
e	759 g/mole

$$W = \frac{1.5\,\text{g}\,(759\,\text{g/mole})}{1.0\,(759\,\text{g/mole})} = 1.5\,\text{g}.$$

EXAMPLE 2: Accurately weigh an amount of Aminophylline USP to obtain 250 mg of anhydrous theophylline. [NOTE—The powdered aminophylline dihydrate weighed contains 0.4% w/w adsorbed moisture as stated in the Certificate of Analysis.]

Equation Factor	Numerical Value
W	weight, in mg, of Aminophylline USP (dihydrate)
a	250 mg of theophylline
b	456 g/mole
d	0.996
e	360 g/mole

$$W = \frac{250\,\text{mg}\,(456\,\text{g/mole})}{0.996\,(360\,\text{g/mole})} = 318\,\text{mg}$$

EXAMPLE 3: Accurately weigh an amount of Lithium Citrate USP (containing 2.5% moisture as stated in the Certificate of Analysis) to obtain 200 mEq of lithium (Li^+). [NOTE—One mEq of Li^+ is equivalent to 0.00694 g of Li^+.]

Equation Factor	Numerical Value
W	weight, in g, of Lithium Citrate USP (tetrahydrate)
a	200 mEq of Li^+ or 1.39 g of Li^+
b	282 g/mole
d	0.975
e	3 × 6.94 g/mole or 20.8 g/mole

$$W = \frac{1.39\,\text{g}\,(282\,\text{g/mole})}{0.975\,(20.8\,\text{g/mole})} = 19.3\,\text{g}.$$

EXAMPLE 4: Accurately weigh an amount of Netilmicin Sulfate USP, equivalent to 2.5 g of netilmicin. [NOTE—Using the procedure under *Loss on Drying* ⟨731⟩, the Netilmicin Sulfate USP that was weighed lost 12% of its weight.]

Equation Factor	Numerical Value
W	weight, in g, of Netilmicin Sulfate USP
a	2.5 g
b	1442 g/mole
d	0.88
e	951 g/mole

$$W = \frac{2.5\,\text{g}\,(1442\,\text{g/mole})}{0.88\,(951\,\text{g/mole})} = 4.31\,\text{g}.$$

Buffer Solutions

Definition—A buffer solution is an aqueous solution that resists a change in pH when small quantities of acid or base are added, when diluted with the solvent, or when the temperature changes. Most buffer solutions are mixtures of a weak acid and one of its salts or mixtures of a weak base and one of its salts. Water and solutions of a neutral salt such as sodium chloride have very little ability to resist the change of pH and are not capable of effective buffer action.

Preparation, Use, and Storage of Buffer Solutions—Buffer solutions for pharmacopeial tests should be prepared using freshly boiled and cooled water (see *Standard Buffer Solutions* under *Buffer Solutions in Reagents, Indicators, and Solutions*). They should be stored in containers such as Type I glass bottles and used within 3 months of preparation.

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Buffers used in physiological systems are carefully chosen so as not to interfere with the pharmacological activity of the medicament or the normal function of the organism. Commonly used buffers in parenteral products, for example, are acetic, citric, glutamic, and phosphoric acids and their salts. Buffer solutions should be freshly prepared.

The Henderson-Hasselbalch equation, noted above, allows the pH of a buffer solution of a weak acid and its salt to be calculated. Appropriately modified, this equation may be applied to buffer solutions composed of a weak base and its salt.

Buffer Capacity—The buffer capacity of a solution is the measurement of the ability of that solution to resist a change in pH upon addition of small quantities of a strong acid or base. An aqueous solution has a buffer capacity of 1 when 1 L of the buffer solution requires 1 gram equivalent of strong acid or base to change the pH by 1 unit. Therefore, the smaller the pH change upon the addition of a specified amount of acid or base, the greater the buffer capacity of the buffer solution. Usually, in analysis, much smaller volumes of buffer are used in order to determine the buffer capacity. An approximate formula for calculating the buffer capacity is gram equivalents of strong acid or base added per L of buffer solution per unit of pH change, i.e., (Eq /L)/(pH change).

EXAMPLE—
The addition of 0.01 g equivalents of sodium hydroxide to 0.25 L of a buffer solution produced a pH change of 0.50. The buffer capacity of the buffer solution is calculated as follows:

$$(0.01/0.25)/0.50 = 0.08(\text{Eq/L})/(\text{pH change})$$

Dosage Calculations

Special Dosage Regimens—Geriatric and pediatric patients require special consideration when designing dosage regimens. In geriatric patients, the organs are often not functioning efficiently as a result of age-related pharmacokinetic changes or disease. For these patients, modifications in dosing regimens are available in references such as *USP Drug Information*.

For pediatric patients, where organs are often not fully developed and functioning, careful consideration must be applied during dosing. Modifications in dosing regimens for pediatric patients are also available in references such as *USP Drug Information*. General rules for calculating doses for infants and children are available in pharmacy calculation textbooks. These rules are not drug-specific and should be used only in the absence of more complete information.

The usual method for calculating a dose for children is to use the information provided for children for the specific drug. The dose is frequently expressed as mg of drug per kg of body weight for a 24-hour period, and is then usually given in divided portions.

The calculation may be made using the following equation:

(mg of drug per kg of body weight) × (kg of body weight) = dose for an individual for a 24-hour period

A less frequently used method of calculating the dose is based on the surface area of the individual's body. The dose is expressed as amount of drug per body surface area in m^2, as shown in the equation below:

(amount of drug per m^2 of body surface area) × (body surface area in m^2) = dose for an individual for a 24-hour period.

The body surface area (BSA) may be determined from nomograms relating height and weight in dosage handbooks. The BSA for adult and pediatric patients may also be determined using the following equations:

$$\text{BSA } (m^2) = \text{square root of } \{[\text{Height (in)} \times \text{Weight (lb)}] / 3131\}$$

or

$$\text{BSA } (m^2) = \text{square root of } \{[\text{Height (cm)} \times \text{Weight (kg)}]/ 3600\}.$$

EXAMPLE—
Rx for Spironolactone Suspension 25 mg/tsp. Sig: 9 mg BID for an 18 month-old child who weighs 22 lbs.

The *USP DI 2002,* 22nd ed., states that the normal pediatric dosing regimen for Spironolactone is 1 to 3 mg per kg per day. In this case, the weight of the child is 22 lbs, which equals 22 lbs/(2.2 lbs/kg) = 10 kg. Therefore the normal dose for this child is 10 to 30 mg per day and the dose ordered is 18 mg per day as a single dose or divided into 2 to 4 doses. The dose is acceptable based on published dosing guidelines.

Percentage Concentrations

Percentage concentrations of solutions are usually expressed in one of three common forms:

$$\text{Volume percent (v/v)} = \frac{\text{Volume of solute}}{\text{Volume of solution}} \times 100\%$$

$$\text{Weight percent (w/w)} = \frac{\text{Weight of solute} \times 100\%}{\text{Weight of solution}}$$

$$\text{Weight in volume percent (w/v)} = \frac{\text{Weight of solute (in g)}}{\text{Volume of solution (in mL)}} \times 100\%$$

See also *Percentage Measurements* under *Concentrations* in the *General Notices*. The above three equations may be used to calculate any one of the three values (i.e., weights, volumes, or percentages) in a given equation if the other two values are known.

Note that weights are always additive, i.e., 50 g plus 25 g = 75 g. Volumes of two different solvents or volumes of solvent plus a solid solute are not strictly additive. Thus 50 mL of water + 50 mL of pure alcohol do not produce a volume of 100 mL. Nevertheless, it is assumed that in some pharmaceutical calculations, volumes are additive, as discussed below under *Reconstitution of Drugs Using Volumes Other than Those on the Label.*

EXAMPLES—

1. Calculate the percentage concentrations (w/w) of the constituents of the solution prepared by dissolving 2.50 g of phenol in 10.00 g of glycerin. Using the weight percent equation above, the calculation is as follows.

   Total weight of the solution = 10.00 g + 2.50 g = 12.50 g.

   Weight percent of phenol = (2.50 g × 100%)/12.50 g = 20.0% of phenol.

   Weight percent of glycerin = (10 g × 100%)/12.50 g = 80.0% of glycerin.

2. A prescription order reads as follows:
   Eucalyptus Oil 3% (v/v) in Mineral Oil.
   Dispense 30.0 mL.
   What quantities should be used for this prescription? Using the volume percent equation above, the calculation is as follows.
   Amount of Eucalyptus Oil:

   $$3\% = (\text{Volume of oil in mL}/30.0\text{ mL}) \times 100\%$$

   Solving the equation, the volume of oil = 0.90 mL
   Amount of Mineral Oil:
   To 0.90 mL of Eucalyptus Oil add sufficient Mineral Oil to prepare 30.0 mL.
3. A prescription order reads as follows:

Zinc oxide	7.5 g
Calamine	7.5 g
Starch	15 g
White petrolatum	30 g

   Calculate the percentage concentration for each of the four components. Using the weight percent equation above, the calculation is as follows.
   Total weight = 7.5 g + 7.5 g + 15 g + 30 g = 60.0 g.
   Weight percent of zinc oxide = (7.5 g zinc oxide/60 g ointment) × 100% = 12.5%.
   Weight percent of calamine = (7.5 g calamine/60 g ointment) × 100% = 12.5%.
   Weight percent of starch = (15 g starch/60 g ointment) × 100% = 25%.
   Weight percent of white petrolatum = (30 g white petrolatum/60 g ointment) × 100% = 50%.

Specific Gravity

The definition of Specific Gravity is usually based on the ratio of weight of a substance in air at 25° to that of the weight of an equal volume of water at the same temperature. The weight of 1 mL of water at 25° is approximately 1 g. The following equation may be used for calculations.

Specific Gravity = (Weight of the substance)/(Weight of an equal volume of water)

EXAMPLES—

1. A liquid weighs 125 g and has a volume of 110 mL. What is the specific gravity?
   The weight of an equal volume of water is 110 g.
   Using the above equation, specific gravity = 125 g/110 g = 1.14.
2. Hydrochloric Acid NF is approximately a 37% (w/w) solution of hydrochloric acid (HCl) in water. How many grams of HCl are contained in 75.0 mL of HCl NF? (Specific gravity of Hydrochloric Acid NF is 1.18.)
   Calculate the weight of HCl NF using the above equation.
   The weight of an equal volume of water is 75 g.
   Specific Gravity 1.18 = weight of the HCl NF g /75.0 g.
   Solving the equation, the weight of HCl NF is 88.5 g.
   Now calculate the weight of HCl using the weight percent equation.
   37.0 % (w/w) = (weight of solute g/88.5 g) × 100.
   Solving the equation, the weight of the HCl is 32.7 g.

Dilution and Concentration

A concentrated solution can be diluted. Powders and other solid mixtures can be triturated or diluted to yield less concentrated forms. Because the amount of solute in the diluted solution or mixture is the same as the amount in the concentrated solution or mixture, the following relationship applies to dilution problems.

The quantity of *Solution 1* (Q_1) × concentration of *Solution 1* (C_1) = the quantity of *Solution 2* (Q_2) × concentration of *Solution 2* (C_2), or

$$(Q_1)(C_1) = (Q_2)(C_2).$$

Almost any quantity and concentration terms may be used. However, the units of the terms must be the same on both sides of the equation.

EXAMPLES—

1. Calculate the ~~amount~~ ■quantity■ 1S *(USP29)* (Q_2), in g, of diluent that must be added to 60 g of a 10% (w/w) ointment to make a 5% (w/w) ointment.
   Let (Q_1) = 60 g, (C_1) = 10%, and (C_2) = 5%.
   Using the above equation,

   $$60\text{ g} \times 10\% = (Q_2) \times 5\%\text{ (w/w)}$$

   Solving the above equation, the ~~amount~~ ■quantity■ 1S *(USP29)* of product needed, Q_2, is 120 g. The initial ~~amount~~ ■quantity■ 1S *(USP29)* of product added was 60 g, and therefore an additional 60 g of diluent must be added to the initial ~~amount~~ ■quantity■ 1S *(USP29)* to give a total of 120 g.
2. How much diluent should be added to 10 g of a trituration (1 in 100) to make a mixture that contains 1 mg of drug in each 10 g of final mixture?
   Determine the final concentration by first converting mg to g. One mg of drug in 10 g of mixture is the same as 0.001g in 10 g.
   Let (Q_1) = 10 g, (C_1) = (1 in 100), and (C_2) = (0.001 in 10).
   Using the equation for dilution, 10 g × (1/100) = (Q_2) g × (0.001/10).
   Solving the above equation, (Q_2) = 1000 g.
   Because 10 g of the final mixture contains all of the drug and some diluent, (1000 g – 10 g) or 990 g of diluent is required to prepare the mixture at a concentration of 0.001 g of drug in 10 g of final mixture.
3. Calculate the percentage strength of a solution obtained by diluting 400 mL of a 5.0% solution to 800 mL.
   Let (Q_1) = 400 mL, (C_1) = 5%, and (Q_2) = 800 mL.
   Using the equation for dilution, 400 mL × 5% = 800 mL × (C_2)%.
   Solving the above equation, (C_2) = 2.5% (w/v).

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Use of Potency Units

See *Units of Potency* in the *General Notices*.

Because some substances may not be able to be defined by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency.

EXAMPLES—

1. One mg of Pancreatin contains not less than 25 USP Units of amylase activity, 2.0 USP Units of lipase activity, and 25 USP Units of protease activity. If the patient takes 0.1 g (100 mg) per day, what is the daily amylase activity ingested?

   1 mg of Pancreatin corresponds to 25 USP Units of amylase activity.

   100 mg of Pancreatin corresponds to 100 × (25 USP Units of amylase activity) = 2500 Units.
2. A dose of penicillin G benzathine for streptococcal infection is 1.2 million units intramuscularly. If a specific product contains 1180 units per mg, how many milligrams would be in the dose?

   1180 units of penicillin G benzathine are contained in 1 mg.

   1 unit is contained in 1/1180 mg.

   1,200,000 units are contained in (1,200,000 × 1)/1180 units = 1017 mg.

Base v. Salt or Ester Forms of Drugs

Frequently the base form of a drug is administered in an altered form such as an ester or salt for stability or other reasons such as taste or solubility. This altered form of the drug usually has a different molecular weight (MW), and at times it may be useful to determine the amount of the base form of the drug in the altered form.

EXAMPLES—

1. Four hundred milligrams of erythromycin ethylsuccinate (molecular weight, 862.1) is administered. Determine the amount of erythromycin (molecular weight, 733.9) in this dose.

   862.1 g of erythromycin ethylsuccinate corresponds to 733.9 g of erythromycin.

   1 g of erythromycin ethylsuccinate corresponds to (733.9/862.1) g of erythromycin.

   0.400 g of erythromycin ethylsuccinate corresponds to (733.9/862.1) × 0.400 g or 0.3405 g of erythromycin.
2. The molecular weight of testosterone cypionate is 412.6 and that of testosterone is 288.4. What is the dose of testosterone cypionate that would be equivalent to 60.0 mg of testosterone?

   288.4 g of testosterone corresponds to 412.6 g of testosterone cypionate.

   1 g of testosterone corresponds to 412.6/288.4 g of testosterone cypionate.

   60.0 mg or 0.0600 g of testosterone corresponds to (412.6/288.4) × 0.0600 = 0.0858 g or 85.8 mg of testosterone cypionate.

Reconstitution of Drugs Using Volumes Other Than Those On The Label

Occasionally it may be necessary to reconstitute a powder in order to provide a suitable drug concentration in the final product. This may be accomplished by estimating the volume of the powder and liquid medium required.

EXAMPLES—

1. If the volume of 250 mg of ceftriaxone sodium is 0.1 mL, how much diluent should be added to 500 mg of ceftriaxone sodium powder to make a suspension having a concentration of 250 mg per mL?

$$500\ \text{mg} \times \frac{1\ \text{mL}}{250\ \text{mg}} = 2\ \text{mL}.$$

~~2.~~

■1S (*USP29*)
Volume of 500 mg of ceftriaxone sodium =

$$500\ \text{mg} \times \frac{0.1\ \text{mL}}{250\ \text{mg}} = 0.2\ \text{mL}$$

~~3.~~

■1S (*USP29*)
Volume of the diluent required = (2 mL of suspension) – (0.2 mL of Ceftriaxone Sodium) = 1.8 mL.

~~4.~~

■2. ■1S (*USP29*)
What is the volume of dry powder cefonicid, if 2.50 mL of diluent is added to 1 g of powder to make a solution having a concentration of 325 mg per mL?

Volume of solution containing 1 g of the powder =

$$1\ \text{g of cefonicid} \times \frac{1000\ \text{mg}}{1\ \text{g}} \times \frac{1\ \text{mL of solution}}{325\ \text{mg of cefonicid}} = 3.08\ \text{mL}$$

Volume of dry powder cefonicid = 3.08 mL of solution – 2.50 mL of diluent = 0.58 mL.

Alligation Alternate and Algebra

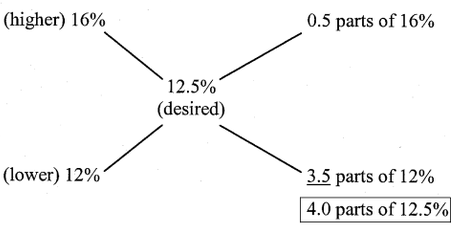
Alligation—Alligation is a rapid method of determining the proportions in which substances of different strengths are mixed to yield a desired strength or concentration. Once the proportion is found, the calculation may be performed to find the exact amounts of substances required. Set up the problem as follows.

1. Place the desired percentage or concentration in the center.
2. Place the percentage of the substance with the lower strength on the lower left-hand side.
3. Place the percentage of the substance with the higher strength on the upper left-hand side.
4. Subtract the desired percentage from the lower percentage, and place the obtained difference on the upper right-hand side.
5. Subtract the higher percentage from the desired percentage, and place the obtained difference on the lower right-hand side.

The results obtained will determine how many parts of the two different percentage strengths should be mixed to produce the desired percentage strength of a drug mixture.

EXAMPLES—

1. How much ointment having a 12% drug concentration and how much ointment having a 16% drug concentration must be used to make 1 kg of a preparation containing a 12.5% drug concentration?



In a total of 4.0 parts of 12.5% product, 3.5 parts of 12% ointment and 0.5 parts of 16% ointment are needed.

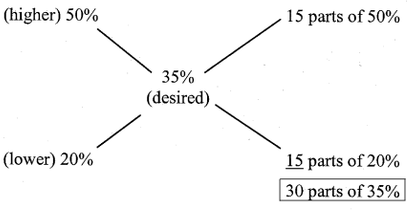
4 parts correspond to 1 kg or 1000 g.

1 part corresponds to 250 g.

3.5 parts correspond to 3.5 × 250 g or 875 g.

0.5 parts correspond to 0.5 × 250 g or 125 g.

2. How many mL of 20% dextrose in water and 50% dextrose in water are needed to make 750 mL of 35% dextrose in water?



In a total of 30 parts of 35% dextrose in water, 15 parts of 50% dextrose in water and 15 parts of 20% dextrose in water are required.

30 parts correspond to 750 mL.

15 parts correspond to 375 mL.

Thus use 375 mL of the 20% solution and 375 mL of the 50% solution to prepare the product.

Algebra—Instead of using alligation to solve the above problems, algebra may be used, following the scheme outlined below.

In order to represent the total ~~amount~~

■quantity■1S *(USP29)*
(weights, parts, or volumes) of the final mixture or solution, 1 or a specified ~~amount~~

■quantity■1S *(USP29)*
is used.

Let x be the ~~amount~~

■quantity■1S *(USP29)*
of one portion and [1 (or the specified amount) – x] be the remaining portion. Set up the equation according to the statement below, and solve.

The amount

■of drug■1S *(USP29)*
in one part plus the amount

■of drug■1S *(USP29)*
in the other part equals the total amount in the final mixture or solution.

EXAMPLES—

1. How much ointment having a 12% drug concentration and how much ointment having a 16% drug concentration must be used to make 1 kg of a preparation containing a 12.5% drug concentration?

   Let 1 kg be the total ~~amount~~

   ■quantity■1S *(USP29)*
   of ointment to be prepared, let x be the quantity, in kg, of the 12% ointment, and let $(1 - x)$ be the quantity in kg of the 16% ointment. The equation is as follows:

   $$(12/100)\,x + (16/100)(1 - x) = (12.5/100)(1).$$

   Solving the equation, x equals 0.875 kg of the 12% ointment and $(1 - x)$ equals $(1 - 0.875)$ or 0.125 kg of the 16% ointment.

2. How many mL of 20% dextrose in water and 50% dextrose in water are needed to make 750 mL of 35% dextrose in water?

   Let x be the volume, in mL, of the 20% solution, and let $(750 - x)$ be the volume in mL of the 50% solution. The equation is as follows:

   $$(20/100)x + (50/100)(750 - x) = (35/100)(750).$$

   Solving the equation, x equals 375 mL of the 20% solution and $(750 - x)$ equals $(750 - 375)$ or 375 mL of the 50% solution.

Molar, Molal, and Normal Concentrations

See *Concentrations* in the *General Notices*.

Molarity—The molar concentration, M, of the solution is the number of moles of the solute contained in one L of solution.

Molality—The molal concentration, m, is the number of moles of the solute contained in one kilogram of solvent.

Normality—The normal concentration, N, of a solution expresses the number of milliequivalents (mEq) of solute contained in 1 mL of solution or the number of equivalents (Eq, gram-equivalent weight) of solute contained in 1 L of solution. When using normality, the pharmacist must apply quantitative chemical analysis principles using molecular weight (MW). Normality depends on the reaction capacity of a chemical compound and therefore the reaction capacity must be known. For acids and bases, reaction capacity is the number of accessible protons available from, or the number of proton binding sites available on, each molecular aggregate. For electron transfer reactions, reaction capacity is the number of electrons gained or lost per molecular aggregate.

EXAMPLES—

1. How much sodium bicarbonate powder is needed to prepare 50.0 mL of a 0.07 N solution of sodium bicarbonate ($NaHCO_3$)? (MW of $NaHCO_3$ is 84.0 g per mol.)

   In an acid or base reaction, because $NaHCO_3$ may act as an acid by giving up one proton, or as a base by accepting one proton, one Eq of $NaHCO_3$ is contained in each mole of

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$NaHCO_3$. Thus the equivalent weight of $NaHCO_3$ is 84 g. [NOTE—The volume, in L, × normality of a solution equals the number of equivalents in the solution.]

The number of equivalents of $NaHCO_3$ required = (0.07 Eq/L) (50.0 mL/1000 mL /L) = 0.0035 equivalents.

1 equivalent weight is 84.0 g.

0.0035 equivalents equals 84.0 g/Eq × 0.0035 Eq = 0.294 g.

2. A prescription calls for 250 mL of a 0.1 N hydrochloric acid (HCl) solution. How many mL of concentrated hydrochloric acid are needed to make this solution? [NOTE—The specific gravity of concentrated hydrochloric acid is 1.18, the molecular weight is 36.46 and the concentration is 37.5% (w/w). Because hydrochloric acid functions as an acid and reacts by giving up one proton in a chemical reaction, 1 Eq is contained in each mole of the compound. Thus the equivalent weight is 36.46 g.]

   The number of equivalents of HCl required is 0.250 L × 0.1 N = 0.025 equivalents.

   1 equivalent is 36.46 g.

   0.025 equivalents correspond to 0.025 Eq × 36.46 g/Eq = 0.9115 g.

   37.5 g of pure HCl are contained in 100 g of concentrated HCl.

   Thus 1 g of pure HCl is contained in (100/37.5) g = 2.666 g of concentrated acid, and 0.9115 g is contained in (0.9115 × 2.666) g or 2.43 g of concentrated acid.

   In order to determine the volume of the supplied acid required, use the definition for specific gravity as shown below.

   Specific gravity = (weight of the substance)/(weight of an equal volume of water).

   1.18 = 2.43 g/(weight of an equal volume of water).

   The weight of an equal volume of water is 2.056 g or 2.06 g, which measures 2.06 mL. Thus, 2.06 mL of concentrated acid is required.

Milliequivalents and Millimoles

NOTE—This section addresses milliequivalents (mEq) and millimoles (mmol) as they apply to electrolytes for dosage calculations.

The quantities of electrolytes administered to patients are usually expressed in terms of mEq. This term must not be confused with a similar term used in quantitative chemical analysis as discussed above. Weight units such as mg or g are not often used for electrolytes because the electrical properties of ions are best expressed as mEq. An equivalent is the weight of a substance (equivalent weight) that supplies one unit of charge. An equivalent weight is the weight, in g, of an atom or radical divided by the valence of the atom or radical. A milliequivalent is one-thousandth of an equivalent (Eq). Because the ionization of phosphate depends on several factors, the concentration is usually expressed in millimoles, moles, or milliosmoles which are described below. [NOTE—Equivalent weight (Eq.wt) = wt. of an atom or radical (ion) in g/valence (or charge) of the atom or radical. Milliequivalent weight (mEq.wt) = Eq.wt. (g)/1000.]

EXAMPLES—

1. Potassium (K^+) has a gram-atomic weight of 39.10. The valence of K^+ is 1^+. Calculate its milliequivalent weight (mEq wt).

   Eq wt = 39.10 g/1 = 39.10 g

   mEq wt = 39.10 g/1000 = 0.03910 g = 39.10 mg

2. Calcium (Ca^{2+}) has a gram-atomic weight of 40.08. Calculate its milliequivalent weight (mEq wt).

   Eq wt = 40.08 g/2 = 20.04 g

   mEq wt. = 20.04 g/1000 = 0.02004 g = 20.04 mg

NOTE—The equivalent weight of a compound may be determined by dividing the molecular weight in g by the product of the valence of either relevant ion and the number of times this ion occurs in one molecule of the compound.

3. How many milliequivalents of potassium ion (K^+) are there in a 250-mg Penicillin V Potassium Tablet? [NOTE—Molecular weight of penicillin V potassium is 388.48 g per mol; there is one potassium atom in the molecule; and the valence of K^+ is 1.]

   Eq wt = 388.48 g/[1(valence) × 1(number of charges)] = 388.48 g.

   mEq wt = 388.48 g/1000 = 0.38848 g = 388.48 mg.

   (250 mg per Tablet)/(388.48 mg per mEq) = 0.644 mEq of K^+ per Tablet.

4. How many equivalents of magnesium ion and sulfate ion are contained in 2 mL of a 50% Magnesium Sulfate Injection? (Molecular weight of $MgSO_4 \cdot 7H_2O$ is 246.48 g per mol.)

   Amount of magnesium sulfate in 2 mL of 50% Magnesium Sulfate Injection

$$2\,\text{mL of Injection} \times \frac{50\,\text{g of magnesium sulfate}}{100\,\text{mL of Injection}} = 1\,\text{g}.$$

   Eq wt of $MgSO_4.7H_2O$ = MW (g)/(valence of specified ion × number of specified ions in one mole of salt).

   For the magnesium ion:

   The number of equivalents is calculated as follows:

   246.48/[2(valence) × 1 (number of ions in the compound)] = 123.24 g/Eq of magnesium ion.

   The number of equivalents in 1 g is 1g/ 123.24 g/Eq = 0.008114 Eq.

   The number of mEq may be calculated as follows.

   The mEq wt = Eq wt (g)/1000 = (123.24 g/Eq)/1000 = 0.12324 g.

   The number of milliequivalents of magnesium ion in 1 g is 1g/ 0.12324 g/mEq = 8.114 mEq.

   For the sulfate ion:

   The number of equivalents is calculated as follows:

   246.48/[2(valence) × 1 (number of ions in the compound)] = 123.24 g/Eq of sulfate ion.

   The number of equivalents in 1 g is 1g/123.24 g/Eq = 0.008114 Eq.

   The number of mEq may be calculated as follows.

   The mEq wt = Eq wt (g)/1000 = (123.24 g/Eq)/1000 = 0.12324 g.

   The number of milliequivalents of sulfate ion in 1 g is 1g/ 0.12324 g/mEq = 8.114 mEq.

5. A vial of Sodium Chloride Injection contains 3 mEq of sodium chloride per mL. What is the percentage strength of this solution? (Molecular weight of sodium chloride is 58.44 g per mol.)

   1 mEq = 1 Eq/1000 = 58.44 g/1000 = 0.05844 g = 58.44 mg.

Amount of sodium chloride in 3 mEq per mL = 58.44 mg per mEq × 3 mEq per mL = 175.32 mg per mL.

$$\frac{175.32\text{ mg}}{1\text{ mL}} = \frac{17532\text{ mg}}{100\text{ mL}} = \frac{17.532\text{ g}}{100\text{ mL}} = 17.5\%$$

Using mols and *mmols*—

A number of countries have adopted the International System of Units and no longer calculate doses using mEq as described above, but instead use the terms moles (mol) and millimoles (mmol). In *USP 28–NF 23,* the International System of Units is used except for the labeling of electrolytes.

Definitions—

A mole equals one gram atomic weight or gram molecular weight of a substance.

A millimole equals 1/1000 of a mole.

EXAMPLES—

1. Potassium (K) has a gram-atomic weight of 39.10. Calculate its weight in millimoles (mmol).

   The weight of one mole is 39.10 g and the weight in millimoles is 39.10 g/1000 =0.0391 g or 39.1 mg.
2. How many millimoles of Penicillin V are in a tablet that contains 250 mg of Penicillin V Potassium? (Molecular weight of penicillin V potassium is 388.48 g per mol.)

   The weight of one mole is 388.48 and the weight in millimoles is 388.48/1000 = 0.3848 g or 388.48 mg. Thus there are 250 mg/388.48 mg/mmol = 0.644 mmol of Penicillin V ion per tablet.

Isoosmotic Solutions

The following discussion and calculations have therapeutic implications in preparations of dosage forms intended for ophthalmic, subcutaneous, intravenous, intrathecal, and neonatal use.

Cells of the body, such as erythrocytes, will neither swell nor shrink when placed in a solution that is isotonic with the body fluids. However, the measurement of tonicity, a physiological property, is somewhat difficult. It is found that a 0.9% (w/v) solution of sodium chloride, which has a freezing point of – 0.52°, is isotonic with body fluids and is said to be isoosmotic with body fluids. In contrast to isotonicity, the freezing point depression is a physical property. Thus many solutions which are isoosmotic with body fluids are not necessarily isotonic with body fluids, e.g., a solution of urea. Nevertheless many pharmaceutical products are prepared using freezing point data or related sodium chloride data to prepare solutions that are isoosmotic with the body fluids. A closely related topic is osmolarity (see *Osmolality and Osmolarity* ⟨785⟩).

Freezing point data or sodium chloride equivalents of pharmaceuticals and excipients (see *Table 1* below) may be used to prepare isoosmotic solutions, as shown in the examples below.

Table 1. Sodium Chloride Equivalents (E) and Freezing Point (FP) Depressions for a 1% Solution of the Drug or Excipient

Drug or Excipient	E	FP Depression
Atropine sulfate	0.13	0.075
Sodium chloride	1.00	0.576

EXAMPLE—

Determine the amount of sodium chloride required to prepare 60 mL of an isoosmotic solution of atropine sulfate 0.5% using the sodium chloride equivalent values and also the freezing point depression values.

Using the sodium chloride equivalent values—

The total amount of substances equivalent to sodium chloride (for a 0.9% solution) = (0.9 g/100 mL) × 60 mL = 0.54 g.

The amount of atropine sulfate required = (0.5 g/100 mL) × 60 mL = 0.3 g.

1 g of atropine sulfate is equivalent to 0.13 g of sodium chloride.

0.3 g atropine sulfate is equivalent to 0.3 × 0.13 g = 0.039 g of sodium chloride.

Thus the required amount of sodium chloride is 0.54 – 0.039 = 0.501 g or 0.50 g.

Using freezing point depression values—

The freezing point depression required is 0.52°.

A 1% solution of atropine sulfate causes a freezing point depression of 0.075°.

A 0.5% solution of atropine sulfate causes a freezing point depression of 0.075° × 0.5 = 0.0375°.

The additional freezing point depression required is 0.52° – 0.0375° = 0.482°.

A 1% solution of sodium chloride causes a freezing point depression of 0.576°.

A (1%/ 0.576) solution of sodium chloride causes a freezing point depression of 1°.

A (1%/ 0.576) × 0.482 = 0.836% solution of sodium chloride causes a freezing point depression of 0.482°.

The required amount of sodium chloride is (0.836 g/100 mL) × 60 mL = 0.502 g or 0.50 g.

Flow Rates in Intravenous Sets

Some calculations concerning flow rates in intravenous sets are provided below. [NOTE—Examples below are *not* to be used for treatment purposes.]

EXAMPLES—

1. Sodium Heparin 8,000 units in 250 mL Sodium Chloride Injection 0.9% solution are to be infused over 4 hours. The administration set delivers 20 drops per mL.

   What is the flow rate in mL per hour?

   In 4 hours, 250 mL are to be delivered.

   In 1 hour, 250 mL/4 = 62.5 mL are delivered.

   What is the flow rate in drops per minute?

   In 60 minutes, 62.5 mL are delivered.

   In 1 minute, 62.5 mL/60 = 1.04 mL are delivered.

   1 mL = 20 drops.

   1.04 mL = 1.04 × 20 drops = 20.8 drops.

   Thus in 1 minute, 20.8 or 21 drops are administered.
2. A 14.5 kg patient is to receive 50 mg of Sodium Nitroprusside in 250 mL of dextrose 5% in water (D5W) at the rate of 1.3 µg per kg per minute. The set delivers 50 drops per mL.

   Calculate the flow rate in mL per hour.

   The dose for 1 kg is 1.3 µg per minute.

   The 14.5 kg patient should receive 14.5 × 1.3 µg = 18.85 µg per minute.

   50 mg or 50000 µg of drug are contained in 250 mL of D5W.

   18.85 µg are contained in 250 mL × 18.85/50000 = 0.09425 mL D5W, which is administered every minute.

   In 1 minute, 0.09425 mL are administered.

In 1 hour or 60 minutes, 60 × 0.09425 mL = 5.655 or 5.7 mL are administered.

Calculate the flow rate in drops per minute.

1 mL corresponds to 50 drops per minute.

0.09425 mL corresponds to 0.09425 × 50 = 4.712 or 4.7 drops per minute.

Temperature

The relationship between Celsius degrees (°C) and Fahrenheit degrees (°F) is expressed by the following equation:

$$9\ (^{\circ}C) = 5\ (^{\circ}F) - 160,$$

in which $^{\circ}C$ and $^{\circ}F$ are the numbers of Celsius degrees and Fahrenheit degrees, respectively.

EXAMPLES—

1. Convert 77 °F to Celsius degrees.
   $9(^{\circ}C) = 5(^{\circ}F) - 160$
   $^{\circ}C = [5(^{\circ}F) - 160]/9 = [(5 \times 77) - 160]/9 = 25\ ^{\circ}C$
2. Convert 30 °C to Fahrenheit degrees.
   $9(^{\circ}C) = 5(^{\circ}F) - 160$
   $^{\circ}F = [9(^{\circ}C) + 160]/5 = [(9 \times 30) + 160]/5 = 86\ ^{\circ}F$

The relationship between the Kelvin and the Celsius scales is expressed by the equation:

$$K = {}^{\circ}C + 273.1,$$

in which K and $^{\circ}C$ are the numbers of Kelvin degrees and Celsius degrees, respectively.

Application of Mean Kinetic Temperature

See *Pharmaceutical Stability* ⟨1150⟩ for the definition of mean kinetic temperature (MKT). MKT is usually higher than the arithmetic mean temperature and is derived from the Arrhenius equation. MKT addresses temperature fluctuations during the storage period of the product. The mean kinetic temperature, T_K, is calculated by the following equation:

$$T_K = \frac{\frac{-\Delta H}{R}}{ln(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + ... + e^{-\Delta H/RT_n}}{n})},$$

in which ΔH is the heat of activation, which equals 83.144 kJ per mol (unless more accurate information is available from experimental studies); R is the universal gas constant, which equals 8.3144×10^{-3} kJ per degree per mol; T_1 is the average temperature, in degrees Kelvin, during the first time period, e.g., the first week; T_2 is the average temperature, in degrees Kelvin, during the second time period, e.g., second week; and T_n is the average temperature, in degrees Kelvin during the nth time period, e.g., nth week, n being the total number of temperatures recorded. The mean kinetic temperature is calculated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded (see *Pharmaceutical Stability* ⟨1150⟩). This calculation can be performed manually with a pocket calculator or electronically with computer software.

EXAMPLES—

1. The means of the highest and lowest temperatures for 52 weeks are 25 °C each. Calculate the MKT.
   $n = 52$
   $\Delta H/R = 10{,}000$ K
   $T_1, T_2, ..., T_n = 25\ ^{\circ}C = 273.1 + 25 = 298.1$ K
   $R = 0.0083144$ kJ $K^{-1}mol^{-1}$
   $\Delta H = 83.144$ kJ per mol

$$T_K = \frac{\frac{-\Delta H}{R}}{ln(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + ... + e^{-\Delta H/RT_n}}{n})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{52 \times e^{-\Delta H/R \times 298.1}}{52})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{52 \times e^{-33.5158}}{52})}$$

$$= \frac{-10{,}000\text{K}}{-33.5458} = 298.1\text{K} = 25.0^{\circ}\text{C}$$

The calculated MKT is 25.0 °C. Therefore the controlled room temperature requirement is met by this pharmacy. [NOTE—If the averages of the highest and lowest weekly temperatures differed from each other and were in the allowed range of 15 °C to 30 °C (see *Controlled Room Temperature* under *Preservation*, *Packaging*, *Storage*, *and Labeling* in the *General Notices*), then each average would be substituted individually into the equation. The remaining two examples illustrate such calculations, except that the monthly averages are used]

2. A pharmacy recorded a yearly MKT on a monthly basis, starting in January and ending in December. Each month, the pharmacy recorded the monthly highest temperature and the monthly lowest temperature, and the average of the two was calculated and recorded for the MKT calculation at the end of the year (see *Table 2*). From these data the MKT may be estimated or it may be calculated. If more than half of the observed temperatures are lower than 25 °C and a mean lower than 23 °C is obtained, the MKT may be estimated without performing the actual calculation.

a. To estimate the MKT, the recorded temperatures are evaluated and the average is calculated. In this case, the calculated arithmetic mean is 22.9 °C. Therefore, the above requirements are met and it can be concluded that the mean kinetic temperature is lower than 25 °C. Therefore, the controlled room temperature requirement is met.

Table 2. Data for Calculation of MKT

n	Month	Lowest Temperature (in °C)	Highest Temperature (in °C)	Average Temperature (in °C)	Average Temperature (in K)	$\Delta H/RT$	$e^{-\Delta H/RT}$
1	Jan.	15	27	21	294.1	34.002	1.710×10^{-15}
2	Feb.	20	25	22.5	295.6	33.830	2.033×10^{-15}
3	Mar.	17	25	21	294.1	34.002	1.710×10^{-15}
4	Apr.	20	25	22.5	295.6	33.830	2.033×10^{-15}
5	May	22	27	24.5	297.6	33.602	2.551×10^{-15}
6	June	15	25	20	293.1	34.118	1.523×10^{-15}
7	July	20	26	23	296.1	33.772	2.152×10^{-15}
8	Aug.	22	26	24	297.1	33.659	2.411×10^{-15}
9	Sept.	23	27	25	298.1	33.546	2.699×10^{-15}
10	Oct.	20	28	24	297.1	33.659	2.411×10^{-15}
11	Nov.	20	24	22	295.1	33.887	1.919×10^{-15}
12	Dec.	22	28	25	298.1	33.546	2.699×10^{-15}

b. The second approach is to perform the actual calculation.

$$n = 12$$

$$T_K = \frac{\frac{-\Delta H}{R}}{ln(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + ... + e^{-\Delta H/RT_n}}{n})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{1.710\times10^{-15} + 2.033\times10^{-15} + 1.710\times10^{-15} + ... + 2.699\times10^{-15}}{12})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{2.585 \times 10^{-14}}{12})}$$

$$= \frac{-10{,}000\text{K}}{-33.771} = 296.11\text{K} = 23.0\ ^\circ\text{C}$$

The calculated MKT is 23.0 °C, so the controlled room temperature requirement is met. [NOTE—These data and calculations are used only as an example.]

3. An article was stored for one year in a pharmacy where the observed monthly average of the highest and lowest temperatures was 25 °C (298.1 K), except for one month with an average of 28 °C (301.1 K). Calculate the MKT of the pharmacy.

$$n = 12$$

$$T_K = \frac{\frac{-\Delta H}{R}}{ln(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + ... + e^{-\Delta H/RT_n}}{n})},$$

$$= \frac{\frac{-\Delta H}{R}}{ln(\frac{11 \times e^{-\Delta H/(R \times 298.1)} + 1 \times e^{-\Delta H/(R \times 301.1)}}{12})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{11 \times e^{-33.546} + 1 \times e^{-33.212}}{12})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{2.9692 \times 10^{-14} + 3.7705 \times 10^{-15}}{12})}$$

$$= \frac{-10{,}000\text{K}}{ln(\frac{3.3463 \times 10^{-14}}{12})}$$

$$= \frac{-10{,}000\text{K}}{ln(2.7886 \times 10^{-15})}$$

$$= \frac{-10{,}000\text{K}}{-33.513} = 298.39\text{K} = 25.29°\text{ C}$$

The controlled room temperature requirement is not met because the calculated MKT exceeds 25 °C. (See *Note* in Example 2 above.)

■4. Using the same calculation technique for controlled room temperature, the MKT for controlled cold temperatures can also be calculated.

a. For example, if the mean of the highest and lowest temperatures for each week over a period of 52 weeks was 8 °C (i.e., the same mean for each week), then the MKT can be calculated as follows:

$$T_K = \frac{-10{,}000}{ln\left[52e^{-\Delta H/R(281.1)}\right]/52}$$

$$T_K = \frac{-10{,}000}{ln\left[e^{-\Delta H/R(281.1)}\right]}$$

$$T_K = \frac{-10{,}000}{ln\left[e^{-35.575}\right]}$$

$$= \frac{-10{,}000}{ln\left[3.548 \times 10^{-16}\right]}$$

$$= \frac{-10{,}000}{-35.575}$$

$T_K = 281.1\text{K}$
$C = 281.1 - 273.1$
$C = 8°$

b. In another example, where a variety of average temperatures are used, as would be the case in reality, if the average of the highest and lowest temperatures ranges from 0° to 15 °C, then these averages would be individually substituted into the equation. For simplification of the mathematical process, 10 intervals are shown in *Table 3* below. This illustration is intended for calculation of MKT at storage or in transit; i.e., during shipping or distribution of the critical drug product. These calculations can be performed manually or with a computer.

Table 3. Sample Data for MKT Calculations

Intervals	Low	High	Average	Average Temperature (°C)	ΔH/RT	$e^{-\Delta H/RT} \times 10^{16}$
1	0	5	2.5	275.6	36.284	1.746
2	2	8	5	278.1	35.958	2.419
3	3	9	6	279.1	35.829	2.752
4	3	14	8.5	281.6	35.511	3.782
5	7	15	11	284.0	35.211	5.106
6	1	6	3.5	276.6	36.153	1.990
7	5	15	10	283.1	35.323	4.565
8	2	14	8	281.1	35.575	3.548
9	2	6	4	277.1	36.088	2.124
10	3	10	6.5	279.6	35.765	2.934

■1S (*USP29*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form, *USP 28* page 2799. It is proposed to correct the procurement information about this reagent.

(HDQ: M. Marques) RTS—42323-1

Change to read:

Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form—Use a suitable grade.

[NOTE—A suitable resin is ~~"AG 50W-X12,"~~ ■"AG 1-X4, catalog number 140-1331,"■1S (*USP29*) produced by BioRad Laboratories, www.bio-rad.com.]

BRIEFING

Dicyclohexyl, *USP 28* page 2813. To facilitate the procurement of this reagent, it is proposed to add its synonym and CAS number.

(HDQ: M. Marques) RTS—42482-1

Change to read:

▲**Dicyclohexyl,** ~~$C_{12}H_{22}$—166.31~~

■*(Bicyclohexyl)* $C_{12}H_{22}$—**166.31** [*92-51-3*]■1S (*USP29*) —Use a suitable grade.▲*USP28*

BRIEFING

Dodecyltrimethylammonium Bromide. This new reagent is used to prepare the *Mobile phase* in the *Assay* in the new monograph *Citalopram Hydrobromide Tablets,* proposed elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41833-2

Add the following:

■**Dodecyltrimethylammonium Bromide** *(Lauryltrimethylammonium bromide).* $CH_3(CH_2)_{11}N(CH_3)_3Br$—**308.3** [*1119-94-4*]—Use a suitable grade.

[NOTE—A suitable grade is available as catalog number D 5047 from www.sigma-aldrich.com.]■1S (*USP29*)

BRIEFING

Ethylene Oxide in Methylene Chloride (50 mg/mL)—It is proposed to add this new reagent that is used to prepare the *Ethylene oxide standard solution* in the test for *Limit of ethylene oxide and dioxane* under *Polyethylene Glycol,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—42266-1

Add the following:

■**Ethylene Oxide in Methylene Chloride (50 mg/mL)**—Use a suitable grade.

[NOTE—A suitable grade is available from Sigma Aldrich Corporation, www.sigmaaldrich.com.]■1S (*NF24*)

Test Solutions

BRIEFING

Test Solutions, *USP 28* page 2855 and page 3338 of the *First Supplement.* Two new *Test Solutions* are proposed: Phenol TS and Alkaline Sodium Citrate TS, both specified in the test for *Limit of ammonia* in the *Potassium Bitartrate, Potassium Sodium Tartrate,* and *Sodium Bicarbonate* monographs published elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—42377-4; 42377-5

Add the following:

■**Phenol TS**—Dissolve 1.2 g of phenol in alcohol to make 10 mL. Prepare weekly.■1S (*USP29*)

Add the following:

■**Sodium Citrate TS, Alkaline**—Dissolve 50 g of sodium citrate dihydrate and 2.5 g of sodium hydroxide in water to make 250 mL.■1S (*USP29*)

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869, page 3346 of the *First Supplement,* and page 589 of *PF* 31(2) [Mar.–Apr. 2005].

(HDQ) RTS—41008-2; 41078-2; 41431-1; 41431-2; 41684-1; 41833-1; 41833-5; 41833-6

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:	
■Benazepril Tablets	W ■2S (*USP28*)
Add the following:	
■Bismuth Subsalicylate Tablets	T ■2S (*USP28*)
Add the following:	
■Cefaclor Tablets	T ■2S (*USP28*)
Add the following:	
■Chromium Picolinate Tablets	W ■2S (*USP28*)
Add the following:	
■Citalopram Hydrobromide Tablets	W ■1S (*USP29*)
Add the following:	
■Clarithromycin Tablets, Extended-Release	W ■2S (*USP28*)
Add the following:	
■Black Cohosh Tablets	T, LR ■2S (*USP28*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W ■2S (*USP28*)
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W ■2S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Fexofenadine Hydrochloride Tablets	W ■2S (*USP28*)
Add the following:	
■Fosinopril Sodium Tablets	T ■2S (*USP28*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T ■2S (*USP28*)
Add the following:	
■Gabapentin Capsules	W ■2S (*USP28*)
Add the following:	
■Ginkgo Capsules	T, LR ■2S (*USP28*)
Add the following:	
■Ginkgo Tablets	T, LR ■2S (*USP28*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■ ■2S (*USP28*)
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR ■1S (*USP29*)
Add the following:	
■Indinavir Sulfate Capsules	T ■2S (*USP28*)
Add the following:	
■Irbesartan Tablets	W ■2S (*USP28*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W ■2S (*USP28*)
Add the following:	
■Isosorbide Mononitrate Tablets	T ■2S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■2S (*USP28*)
Add the following:	
■Lysine Hydrochloride Tablets	W■2S (*USP28*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S (*USP29*)
Add the following:	
■Modafinil Tablets	T■2S (*USP28*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■2S (*USP28*)
Add the following:	
■Omeprazole Capsules, Delayed-Release	T, LR■2S (*USP28*)
Add the following:	
■Oxaprozin Tablets	T, LR■2S (*USP28*)
Add the following:	
■Quinapril Tablets	W■2S (*USP28*)
Add the following:	
▲Tizanidine Tablets	T▲*USP29*
Add the following:	
■Valerian Capsules	T, LR■2S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■2S (*USP28*)
Add the following:	
▲Zinc Sulfate Tablets	W▲*USP29*

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 3347 of the *First Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1236 of *PF* 28(4) [Sept.–Oct. 2002], page 1542 of *PF* 28(5) [Sept.–Oct. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 267 of *PF* 29(1) [Jan.–Feb. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 2057 of *PF* 29(6) [Nov.–Dec. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1050 of *PF* 30(3) [May–June 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], and page 591 of *PF* 31(2) [Mar.–Apr. 2005].

(HDQ) RTS—41225-1; 42425-1; 42290-1; 41672-2; 42386-1; 42222-1; 42222-2; 42222-3; 41833-1; 41833-3; 41833-4; 41451-1

Change to read:

Benzyl Alcohol: Clear, colorless, oily liquid. Boils at about 206°, without decomposition. Is neutral to litmus. Sparingly soluble in water; freely soluble in 50% alcohol. Miscible with alcohol, with ether, and with chloroform.

■The specific gravity is between 1.042 and 1.047.■1S (*NF24*)
NF category: Antimicrobial preservative.

Add the following:

■**Bicalutamide**: White, crystalline powder. Soluble in acetone and in tetrahydrofuran; sparingly soluble in methanol; slightly soluble in chloroform and in absolute alcohol; practically insoluble in hot water.■1S (*USP29*)

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Add the following:

■**Citalopram Hydrobromide:** White to almost white, crystalline powder. Freely soluble in water, in alcohol, and in chloroform.■1S (*USP29*)

Add the following:

■**Gamma Cyclodextrin:** White or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol. *NF category:* Sequestering agent.■1S (*NF24*)

Add the following:

■**Drospirenone:** White to off-white powder. Freely soluble in methylene chloride; soluble in acetone and in methanol; sparingly soluble in ethyl acetate and in alcohol; practically insoluble in hexane and in water.■1S (*USP29*)

Add the following:

■**Fenofibrate:** A white or almost white, crystralline powder. Very soluble in methylene chloride; slightly soluble in alcohol; practically insoluble in water.■1S (*USP29*)

Change to read:

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 in dilute acids.~~

■■1S (*USP29*)

Add the following:

■**Ritonavir:** Freely soluble in methanol and in methylene chloride; very soluble in acetonitrile; practically insoluble in water.■1S (*USP29*)

In-Process Revision

Pending Proposals

(Items from earlier numbers of PF that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA*. Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Cancelled Proposals* list. There are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 30(1) through 30(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF*.

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
General Notices—*Preservation, Packaging, Storage, and Labeling; Tests and Assays; Residual Solvents (delayed implementation to January 1, 2007); Preservation, Packaging, Storage, and Labeling (Poison Prevention Packaging Act)*	30	5	1571
<u>*USP Monographs*</u>			
Acetaminophen Oral Suspension—*USP Reference standards [*add *USP 4-Aminophenol RS], Limit of 4-aminophenol* (add)	30	5	1579
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following–Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid—*Limit of hydroxylamine*	30	5	1579
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Acyclovir—*Assay and limit for guanine*	30	5	1580
Medical Air—*Assay*	28	4	1065
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albumin Human—*Definition, Expiration date, USP Reference standard,* (add), *Identification A, B* (add), *pH* (add), *Molecular size distribution* (add), *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add), *Packaging and storage, Labeling, Bacterial endotoxins* (add), *Sterility* (add), *Heat sterility* (add), *Safety* (add)	29	4	992
Albuterol Tablets—*Dissolution*	31	1	40
Alcohol (new) [Harmonization]	30	5	1844
Dehydrated Alcohol (new) [Harmonization]	30	5	1848
Alcohol in Dextrose Injection—*Assay for dextrose*	30	5	1581
Allopurinol—*USP Reference standards, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	28	5	1386
Alprazolam Tablets—*Identification, Dissolution*	30	5	1582
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Amifostine—*Related compounds*	30	6	1974
Amifostine for Injection—*Related compounds*	30	6	1976
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amoxicillin Capsules—*Dissolution*	30	5	1583
Amoxicillin Tablets—*Dissolution*	30	6	1977
Amphetamine Sulfate—*Assay*	31	2	381
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Anticoagulant Citrate Dextrose Solution—*Assay for dextrose*	30	5	1583

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Benazepril Hydrochloride (new)	29	5	1422
Benazepril Hydrochloride Tablets (new)	29	3	606
Betahistine Hydrochloride (new)	30	5	1584
Betamethasone Acetate—*Identification B*	31	2	381
Betamethasone Tablets—*Dissolution*	30	1	62
Bethanechol Chloride—*Related compounds, Assay*	30	5	1586
Bethanechol Chloride Tablets—*Related compounds, Assay*	30	5	1587
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Bismuth Subsalicylate Oral Suspension (new)	30	4	1166
Bismuth Subsalicylate Tablets (new)	30	4	1167
Bretylium Tosylate in Dextrose Injection—*Assay for dextrose*	30	5	1589
Brompheniramine Maleate Tablets—*Dissolution*	30	6	1978
Budesonide (new)	30	6	1978
Bupivacaine Hydrochloride—*Limit of residual solvents*	30	5	1589
Bupivacaine Hydrochloride in Dextrose Injection—*Assay for dextrose*	30	5	1590
Bupropion Hydrochloride—*Chromatographic purity*	31	2	381
Bupropion Hydrochloride Extended-Release Tablets—*USP Reference standards, Related compounds*	31	2	384
Butabarbital Sodium Tablets—*Uniformity of dosage units*	31	1	41
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Caffeine Citrate Injection—*Definition, Related compounds, Assay*	30	5	1590
Caffeine Citrate Oral Solution—*Definition, Related compounds, Assay*	30	5	1593
Calcitonin Salmon (new)	31	2	385
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	29	5	1433
Calcitriol Injection (new)	29	5	1434
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Carboxymethylcellulose Sodium Suspension (new)	30	3	812
Cefaclor Tablets (new)	29	6	1858
Cefaclor Extended-Release Tablets—*Labeling* (delete)	31	1	42
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Ciclopirox Olamine Cream—*USP Reference standards [USP Benzyl Alcohol RS], Content of benzyl alcohol*	30	5	1595
Ciclopirox Olamine Topical Suspension—*USP Reference standards [USP Benzyl Alcohol RS]*	30	5	1596
Ciprofloxacin—*USP Reference standards, Other requirements*	31	2	393
Ciprofloxacin Injection—*Definition, USP Reference standards, Pyrogen* (delete), *Bacterial endotoxins* (add), *Limit of ciprofloxacin ethylenediamine analog, Dextrose content*	31	2	393
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid*	31	2	394
Anhydrous Citric Acid [Harmonization]—*Packaging and storage, Organic volatile impurities* (delete)	31	2	607
Citric Acid Monohydrate [Harmonization]—*Packaging and storage, Color of solution*	30	5	1854
Cladribine (new)	31	2	395
Clarithromycin—*Definition, USP Reference standards, Identification, Specific rotation, pH, Residue on ignition, Heavy metals, Related substances* (add), *Assay*	30	4	1179
Clarithromycin Tablets—*Assay*	30	4	1182
Clarithromycin Extended-Release Tablets (new)	30	4	1183
Clindamycin Injection—*USP Reference standards [USP Benzyl Alcohol RS], Assay*	30	5	1597
Clorazepate Dipotassium—*USP Reference standards, Related compounds*	30	6	1982
Clotrimazole Lozenges—*Disintegration* (delete), *Dissolution* (add)	31	2	398
Clozapine—*Chromatographic purity*	30	6	1984
Codeine Phosphate—*Packaging and storage*	30	5	1597
Colchicine Tablets—*Dissolution*	30	1	91
Cyclandelate (new)	30	6	1985
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Cysteine Hydrochloride—*Assay*	30	5	1598
Dalteparin Sodium (new)	30	5	1598
Cryopreserved Human Fibroblast-Derived Dermal Substitute (new)	30	4	1211
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Dextroamphetamine Sulfate Elixir (delete monograph)	30	5	1612
Dextroamphetamine Sulfate Oral Solution (delete monograph)	30	5	1643
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Dextrose Injection—*Assay*	30	5	1614
Dextrose and Sodium Chloride Injection—*Assay for dextrose*	30	5	1614
Dibucaine—*Identification B*	31	2	399
Dibucaine Cream—*Identification, Assay*	31	2	399
Dibucaine Ointment—*Identification*	31	2	400
Dibucaine Hydrochloride—*Labeling* (add), *USP Reference standards, Identification B, Other requirements* (add)	31	2	400
Dibucaine Hydrochloride Injection—*Identification A*	31	2	401
Diclofenac Sodium Delayed-Release Tablets—*Drug release*	30	6	1986
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add), *Assay*	29	6	1870
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Extended-Release Capsules—*Drug release, Test 14*	30	2	478
Dimercaprol Injection—*USP Reference standards* (add), *Bacterial endotoxins* (add)	30	6	1987
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Uniformity of dosage units*	30	6	1987
Dobutamine in Dextrose Injection—*Assay for dextrose*	30	5	1615
Dopamine Hydrochloride and Dextrose Injection—*Assay for dextrose*	30	5	1615
Dorzolamide Hydrochloride—*Limit of dorzolamide hydrochloride related compound A, Assay*	31	2	401
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride Capsules—*Identification*	30	6	1987
Dyclonine Hydrochloride—*Identification B*	31	1	42
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Egg Phospholipids (new)	29	2	401
Multiple Electrolytes and Dextrose Injection Type 1—*Assay for dextrose*	30	5	1616
Enalapril Maleate and Hydrochlorothiazide Tablets—*Dissolution*	30	6	1988
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	29	6	1882
Epinephrine Injection—*Identification A, B*	31	1	43

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Ergotamine Tartrate and Caffeine Suppositories—*Identification B*	30	6	1988
Ergotamine Tartrate and Caffeine Tablets—*Identification B*	30	6	1988
Estradiol and Norethindrone Acetate Tablets (new)	30	6	1989
Estradiol Transdermal System (new)	30	4	1201
Conjugated Estrogens—*Definition*	30	3	840
Ethacrynic Acid Tablets—*Dissolution*	30	6	1993
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102
Etidronate Disodium—*USP Reference standards [USP Etidronate Disodium Related Compound A RS], Limit of phosphite, Assay*	30	5	1616
Etidronate Disodium Tablets—*Dissolution, Assay*	30	5	1619
Famotidine for Oral Suspension (new)	30	6	1993
Famotidine Tablets—*Related compounds, Assay*	30	6	1995
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Finasteride Tablets—*Dissolution*	30	5	1620
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Related compounds*	31	2	408
Flucytosine—*Fluorouracil*	30	5	1621
Fludarabine Phosphate—*Chloride, Assay*	30	5	1621
Fluoxetine Delayed-Release Capsules (new)	30	3	849
Fluvastatin Capsules (new)	31	1	47
Fluvastatin Sodium (new)	31	1	43
Fluvoxamine Maleate Tablets (new)	30	5	1622
Fosinopril Sodium (new)	30	6	2001
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Gabapentin Capsules (new)	28	7	298
Glyburide Tablets—*Dissolution*	29	2	418
Glycopyrrolate Tablets—*Dissolution*	30	1	105
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	2	410
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Helium—*Identification, Assay*	28	4	1121
Hydrocodone Bitartrate—*USP Reference standards [USP Hydrocodone Bitartrate Related Compound A RS], Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydrogen Peroxide Concentrate—*Acidity*	30	5	1629
Indinavir Sulfate Capsules (new)	30	2	508
Indocyanine Green—*Definition, Assay*	29	6	1905
Insulin Human Injection—*Limit of high molecular weight proteins* (add), *Other requirements*	30	5	1630
Iodixanol—*Labeling* (add), *USP Reference standards, Limit of calcium, Other requirements* (add)	31	1	54
Irbesartan Tablets (new)	29	4	1035
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
Diluted Isosorbide Mononitrate (new)	30	3	868
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	30	3	871
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Lamivudine—*Limit of lamivudine enantiomer, Resolution solution, Limit of residual solvents*	30	3	881
Lansoprazole—*Packaging and storage, Chromatographic purity*	30	6	2010
Leuprolide Acetate (new)	30	3	882
Levothyroxine Sodium—*Assay*	30	5	1630
Levothyroxine Sodium Tablets—*Dissolution, Limit of liothyronine sodium*	31	2	413
Lidocaine Hydrochloride—*Assay*	31	2	415
Lidocaine Hydrochloride and Dextrose Injection—*Assay for dextrose*	30	5	1631
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	31	2	415
Liothyronine Sodium—*Assay*	30	5	1631
Lipid Injectable Emulsion (new)	31	2	416
Liotrix Tablets—*Assay*	30	5	1632
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution, Assay*	30	5	1633
Loratadine—*Labeling* (add), *USP Reference standards, Related compounds*	30	6	2011
Loratadine Oral Solution—*Antimicrobial effectiveness test* (delete), *Related compounds*	31	1	56
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	419

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	26	4	1050
Magnesium Chloride—*Identification, Insoluble matter*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	421
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Mangafodipir Trisodium—*Packaging and storage*	30	6	2014
Mannitol Injection—*Labeling*	28	1	73
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Mefloquine Hydrochloride (new)	31	2	422
Meloxicam (new)	31	1	57
Meperidine Hydrochloride—*Packaging and storage, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	62
Mephobarbital—*Assay*	30	5	1634
Mepivacaine Hydrochloride Injection—*Assay*	30	6	2017
Meprobamate Tablets—*Dissolution*	30	1	129
Mesalamine—*Related compounds*	31	2	424
Metformin Hydrochloride—*Packaging and storage*	31	1	62
Methenamine Tablets—*Dissolution*	30	1	130
Methenamine Hippurate Tablets—*Labeling* (add), *Dissolution*	31	1	63
Methocarbamol Tablets—*Dissolution*	30	1	130
Methscopolamine Bromide (new)	31	2	425
Methscopolamine Bromide Tablets (new)	31	2	427
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Metolazone Tablets—*Assay*	29	6	1932
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate (new)	30	6	2017
Morphine Sulfate—*Packaging and storage*	30	5	1639
Morphine Sulfate Extended-Release Capsules—*Packaging and storage*	28	6	1822
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Nabumetone—*Related compounds*	31	1	63
Nabumetone Tablets—*Dissolution*	30	6	2019
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nalidixic Acid—*Assay*	30	1	132
Naltrexone Hydrochloride—*Limit of total solvents*	30	6	2019
Naproxen Delayed-Release Tablets—*Packaging and storage*	30	4	1264

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

	PF Volume, Issue, and Page Numbers of Pending Proposals		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Nitrous Oxide—*Identification, Assay*	28	4	1169
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Nystatin—*Composition* (add)	30	1	141
Nystatin, Neomycin Sulfate, Thiostrepton, and Triamcinolone Acetonide Ointment—*Assay for nystatin*	30	6	2020
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole Delayed-Release Capsules—*Packaging and storage*	30	1	143
Ondansetron (new)	30	6	2021
Ondansetron Oral Solution—*Packaging and storage*	30	3	905
Ondansetron Orally Disintegrating Tablets (new)	30	6	2024
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new)	30	4	1276
Oxycodone Hydrochloride—*Limit of alcohol*	30	6	2027
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Oxygen—*Identification, Assay*	28	4	1171
Oxygen 93 Percent—*Identification A, B* (delete), *Identification* (add), *Assay*	28	4	1171
Paroxetine Tablets—*Identification A, C*	31	2	435
Paroxetine Hydrochloride—*USP Reference standards, Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine, Chromatographic purity*	31	1	69
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	72
Pentobarbital Sodium—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Perflutren Protein-Type A Microspheres for Injection—*Assay for protein [Footnote 9]*	30	5	1639
Perflutren Protein-Type A Microspheres Injectable Suspension—*Assay for protein [Footnote 9]*	30	5	1640
Petrolatum (new) [Harmonization]	28	2	569
White Petrolatum (new) [Harmonization]	28	2	570
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160

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Phenylephrine Bitartrate (new)	30	6	2028
Phenylethyl Alcohol—*USP Reference standards*	30	4	1290
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Phenytoin Sodium—*Related compounds, Assay*	30	6	2030
Physostigmine Salicylate Injection—*USP Reference standards, Assay*	30	6	2031
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	440
Potassium Bromide (new)	31	2	441
Potassium Chloride in Dextrose Injection—*Definition, Assay for dextrose*	30	5	1640
Potassium Chloride in Dextrose and Sodium Chloride Injection—*Assay for dextrose*	30	5	1641
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate* (delayed implementation)	31	2	444
Prednisolone—*Chromatographic purity* (add), *Ordinary impurities* (delete)	30	5	1641
Prednisolone Acetate—*Identification C*	30	5	1642
Prilocaine (new)	30	5	1643
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propofol—*Packaging and storage, Labeling, USP Reference standards, Related compounds, Assay*	30	5	1645
Propoxycaine Hydrochloride—*Identification C*	30	6	2032
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Quinapril Tablets—*Packaging and storage*	29	4	1071
Ramipril—*Definition, Assay*	30	6	2032
Ranitidine Hydrochloride—*USP Reference standards [USP Ranitidine Resolution Mixture RS], Chromatographic purity, Assay*	30	6	2033

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Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
Oral Rehydration Salts—*USP Reference standards* (add), *Assay for dextrose, Assay for citrate*	31	2	445
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Ringer's and Dextrose Injection—*Assay for dextrose*	30	5	1647
Ropivacaine Hydrochloride (new)	30	6	2039
Saccharin Calcium (new) [Harmonization]	36	2	607
Saccharin Sodium (new) [Harmonization]	36	2	612
Sargramostim—*Definition*	30	6	2044
Scopolamine Hydrobromide—*Identification A*	31	1	73
Sevoflurane (new)	30	1	178
Simvastatin—*Packaging and storage*	30	5	1647
Human Fibroblast-Derived Temporary Skin Substitute (new)	30	4	1211
Sodium Bromide (new)	31	2	446
Sodium Chloride and Dextrose Tablets—*Assay for dextrose*	30	5	1647
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Sotalol Hydrochloride—*Related compounds*	30	6	2044
Soybean Oil—*Definition, Labeling* (add)	30	5	1648
Spironolactone Oral Suspension (new)	30	3	929
Spironolactone Tablets—*Assay*	31	1	74
Spironolactone and Hydrochlorothiazide Oral Suspension (new)	30	3	930
Stavudine—*Packaging and storage*	30	3	932
Succinylcholine Chloride—*Chromatographic purity*	31	1	74
Sufentanil Citrate Injection—*Identification A*	30	6	2045
Sumatriptan Nasal Spray (new)	30	6	2045
Talc (new) [Harmonization]	30	5	1859
Technetium 99Tc Fanolesomab Injection (new)	31	2	448
Terbutaline Sulfate—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	75
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Terbutaline Sulfate Tablets—*USP Reference standards, Dissolution*	31	1	76
Testosterone Enanthate—*Water*	30	5	1648
Tetracaine Hydrochloride—*Identification A*	31	2	451
Tetracaine Hydrochloride in Dextrose Injection—*Assay for dextrose*	30	5	1648
Thalidomide—*Chromatographic purity*	31	2	452
Theophylline in Dextrose Injection—*Assay for dextrose*	30	5	1649

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Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Thioguanine—*Definition, Nitrogen content, Limit of guanine* (add), *Assay*	30	6	2049
Tiagabine Hydrochloride—*Chromatographic purity*	30	5	1649
Tiamulin (new)	31	1	77
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Titanium Dioxide (NL to come)—*New Monograph [UV Attenuation]*	30	4	1304
Tizanidine Tablets (new)	31	2	456
Tizanidine Hydrochloride (new)	31	2	452
Tolcapone—*Definition, Absorptivity, Related compounds*	30	6	2051
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate*	31	2	465
Triclosan—*USP Reference standards, Limit of monochlorophenols and 2,4-dichlorophenol, Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran*	30	6	2054
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Ursodiol Capsules—*Dissolution*	31	1	79
Valsartan (new)	29	6	1996
Valsartan and Hydrochlorothiazide Tablets (new)	29	6	2000
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add), *Chromatographic purity*	30	6	2055
Vecuronium Bromide (new)	30	6	2057
Purified Water—*Definition*	31	2	467
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins, Oxidizable substances*	31	2	468
Water for Injection—*Definition, Bacterial endotoxins*	31	2	466
Small Intestinal Submucosa Wound Matrix (new)	30	5	1652
Zinc Oxide—*Iron and other heavy metals*	31	1	80
Zinc Oxide Neutral (new)	31	1	80
Zinc Sulfate Oral Solution (new)	31	2	468

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Zinc Sulfate Tablets (new)	31	1	82
Dietary Supplements Monographs			
Ademetionine Disulfate Tosylate (new)	31	2	469
Choline Chloride—*Limit of total amines*	31	1	84
Chondroitin Sulfate Sodium Tablets—*Labeling*	31	1	85
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Chondroitin Sulfate Sodium—*Labeling*	30	6	2068
Chondroitin Sulfate Sodium Tablets—*Labeling*	30	6	2071
Chromium Picolinate Tablets (new)	30	5	1664
Echinacea angustifolia—Microbial limits (add)	30	2	552
Ginger Capsules (new)	28	3	814
Powdered Ginkgo Extract (new)	27	2	2233
Ginkgo Capsules (new)	27	2	2238
Ginkgo Tablets (new)	27	2	2240
American Ginseng Capsules (new)	30	2	565
American Ginseng Tablets—*Dissolution [to come]*	30	2	567
Asian Ginseng—*Microbial limits*	30	2	569
Asian Ginseng Capsules (new)	30	2	571
Eleuthero—*Microbial limits*	26	6	1596
Glucosamine and Chondroitin Sulfate Sodium Tablets—*Labeling*	31	1	85
Goldenseal—*Microbial limits*	30	3	952
Licorice—*Microbial limits*	26	5	1363
Powdered Licorice Extract—*Microbial limits*	30	2	574
Lycopene (new)	30	6	2073
Lycopene Preparation (new)	30	6	2075
Lysine Hydrochloride Tablets (new)	30	5	1665
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Psyllium Husk—*Definition, Light extraneous matter, Heavy extraneous matter* (delete)	30	6	2077
Pygeum Extract—*Packaging and storage*	30	3	956
Selenomethionine—*USP Reference standards, Assay*	31	2	482
Tomato Extract Containing Lycopene (new)	30	2	578
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian Capsules (new)	27	1	1825

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USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition*	31	2	504
⟨1⟩ Injections—*Packaging* [Harmonization]	31	1	192
⟨11⟩ USP Reference Standards—	26	3	793
	26	4	1101
	26	5	1369
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	4	1224
	28	5	1468
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	29	3	710
	29	4	1137
	29	5	1601
	29	6	2022
	30	1	211
	30	2	613
	30	3	998
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
⟨41⟩ Weights and Balances—*Introduction, Weights, Balances*	31	2	508
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests [Harmonization]—*Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) [Harmonization]—*Title, Introduction,General Procedures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Introduction, Rabbit Blood Sugar Method—Quantitative, Diluent, Standard Stock Solution, Standard Solutions, Assay Stock Solution, Assay Solutions, Procedure, Blood Samples, Calculation, Appendix* (add)	30	5	1675
⟨267⟩ Porosimetry by Mercury Intrusion (new)	29	3	712
⟨341⟩ Antimicrobial Agents—Contents—*General Gas Chromatographic Method, Polarographic Method*	30	5	1678
⟨345⟩Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures* [delayed implementation]	30	1	220
⟨386⟩ Environmentally Sensitive Preparations (new)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) [Harmonization]	28	3	895
⟨611⟩ Alcohol Determination—*Method II–Gas-Liquid Chromatographic Method, System Suitability Test*	30	4	1379
⟨616⟩ Bulk Density and Tapped Density [Harmonization]	28	3	901

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⟨621⟩ Chromatography—*Introduction, Thin-Layer, Chromatography, Interpretation of Chromatograms, Glossary of Symbols, System Suitability, Chromatographic Reagents*	30	6	2094
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain-coated Tablets* (delete)	30	1	234
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	30	6	2235
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨776⟩ Optical Microscopy (new) [Harmonization]	30	6	2212
⟨785⟩ Osmolality and Osmolarity—*Measurement of Osmolality*	30	5	1702
⟨786⟩ Particle Size Distribution Estimation by Analytical Sieving (new) [Harmonization]	30	6	2216
⟨811⟩ Powder Fineness—*Title, Introduction* (add) [Harmonization]	31	1	228
⟨841⟩ Specific Gravity—*Introduction, Method I, Method II* (add)	31	2	515
⟨851⟩ Spectrophotometry and Light-Scattering—*Procedure*	30	5	1703
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
General Information Chapters			
⟨1065⟩ Ion Chromatography (new)	31	2	519
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1075⟩ Good Compounding Practices—*Introduction, Applicable Definitions, Responsibilities of the Compounder, Training, Procedures and Documentation, Drug Compounding Facilities, Drug Compounding Equipment, Component Selection Requirements, Packaging and Drug Product Containers, Compounding Controls, Labeling, Records and Reports, Compounding for a Prescriber's Office Use, Compounding Veterinarian Products, Compounding Pharmacy Generated Products* (delete)	31	1	101
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1079⟩ Good Storage and Shipping Practices (new)	30	6	2118
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	28	5	1650
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1101⟩ Medicine Dropper—*Introduction*	30	6	2137
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733

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⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709
⟨1116⟩ Microbiological Evaluation of Clean rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add), *Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1119⟩ Near-Infrared Spectrophotometry—*Instrumentation*	30	6	2137
⟨1120⟩ Raman Spectrophotometry (new)	30	6	2139
⟨1136⟩ Packaging—Unit-of-Use (new)	30	5	1722
⟨1174⟩ Powder Flow (new) [Harmonization]	30	6	2226
⟨1177⟩ Good Packaging Practices (new)	30	6	2152
⟨1178⟩ Good Repackaging Practices (new)	30	6	2156
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1216⟩ Tablet Friability [Harmonization]—*Introduction and text*	30	5	1740
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	29	1	256
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1231⟩ Water for Pharmaceutical Purposes (new)	30	5	1744
⟨1232⟩ Instrumentation for Analysis of High Purity Pharmaceutical Waters (new)	30	5	1806
⟨1265⟩ Written Prescription Drug Information—Guidelines (new)	30	3	1040

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⟨2023⟩ Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements—*Supplement Components, Microbiological Testing*	30	5	1818
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
⟨2091⟩ Weight Variation of Nutritional Supplements—*Title, Introduction, Weight Variation, Content Uniformity* (add), *Procedure for Botanical Intake Units* (add)	28	5	1548
Reagent Specifications			
Acetal	30	2	644
Acetanilde	31	2	572
Acetyl Chloride	31	2	573
Acetylcholine Chloride	31	2	573
Air-Nitrous Oxide Certified Standard	28	4	1233
4-Amino-6-chloro-1,3-benzenedisulfonamide	31	2	573
Amyl Acetate	31	2	574
tert-Amyl Alcohol	31	2	574
L-Asparagine	31	2	574
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (add)	29	1	265
Benzaldehyde	31	2	574
Benzphetamine Hydrochloride	31	2	575
Benzyltrimethylammonium Chloride	31	2	575
Biphenyl	31	2	575
N-Bromosuccinimide	31	2	575
2,3-Butanedione	31	2	576
n-Butyl Chloride	31	2	576
Cadmium Acetate	31	2	576
Calcium Citrate	31	2	577
Calcium Lactate	31	2	577
Calf Thymus DNA	30	4	1389
Casein	31	2	578
Charcoal, Activated	31	2	578
Chlorobenzene	31	2	578
4-Chlorophenol (delete)	30	6	2168
Chromotrope 2R	30	4	1390
Citric Acid	30	3	1044
Citric Acid, Anhydrous	30	3	1044
Collagen	30	4	1390
Rat Tail Collagen	30	2	644
Collagenase	30	4	1390
Congo Red	31	2	578

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Cyclohexanol	31	2	579
Deuterated Methanol (new)	29	6	2054
o-Dichlorobenzene	31	2	579
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl Phthalate (add)	26	2	504
Dicyclohexylamine	31	2	579
Diidofluorescein	31	2	579
DEAE-Agarose (add)	29	1	265
1,2-Dimethoxyethane	31	2	580
N,N-Dimethyldodecylamine-*N*-oxide (add)	27	4	2837
Ethyl Cyanoacetate	31	2	580
Ethylene Glycol	31	2	580
Fast Green FCF	30	4	1391
Ferric Ammonium Citrate	31	2	581
Guaiacol	31	2	581
Heptakis (2,6-di-*O*-methyl)-β-cyclodextrin (new)	30	6	2169
n-Heptane, Chromatographic	31	2	581
Hexadimethrine Bromide (add)	29	1	265
Hexamethyldisilazane	31	2	581
Hexane, Solvent	31	2	582
2′-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5′-bi-1*H*-benzimidazole Trihydrochloride Pentahydrate	30	4	1391
Inositol	31	2	582
Isoferulic Acid (add)	27	4	2837
Isopropylamine	31	2	582
Lanthanum Oxide (add)	28	3	851
Maleic Acid	31	2	583
Methyl Acetate	31	2	583
4-Methylpentan-2-ol	30	2	646
Methyl Red (add)	31	1	108
1-Naphthol	31	2	583
2-Naphthol	31	2	583
5-Nitro-1,10-phenanthroline	31	2	584
Nonylphenoxypoly(ethyleneoxy)ethanol	31	2	584
Para-aminobenzoic Acid	31	2	584
Paraformaldehyde	31	2	584
Piperazine (new)	30	5	1821

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Propionic Anhydride	31	2	585
Pyrrole	31	2	585
Direct Red 80	30	4	1390
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Rose Bengal Sodium	31	2	585
Thrombin Human (new)	29	6	2055
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium [Harmonization]	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium [Harmonization]	31	2	613
Silver Oxide	31	2	585
Sodium Arsenite	31	2	586
Sodium Chromate	31	2	586
Sodium Glycocholate	31	2	587
Sodium 1-Hexanesulfonate Monohydrate (new)	31	2	587
Tetramethylammonium Hydroxide	31	2	587
Thioglycolic Acid	31	2	587
Thymol	31	2	588
n-Tricosane	31	2	588
Triethylamine	31	2	588
2,4,6-Trimethylpyridine	31	2	588
Vinyl Acetate	30	6	2169
1-Vinyl-2-pyrrolidone	31	1	108
Zinc Sulfate Heptahydrate (add)	26	2	504
Volumetric Solutions			
Ceric Sulfate, Tenth-Normal (0.1 N)	31	1	109
Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol	31	1	112
Reference Tables			
Container Specifications	31	2	589
Excipients, USP and NF Excipients, Listed by Categories	29	4	1088
	29	6	2008
	30	4	1317
	30	5	1659
	30	6	2062
Description and Solubility	25	4	8589

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	25	6	9254
	26	4	1135
	27	1	1908
	28	2	554
	28	4	1236
	28	5	1542
	28	6	1953
	29	1	266
	29	4	1262
	29	5	1684
	29	6	2057
	30	3	1050
	30	4	1405
	30	5	1822
	30	6	2183
	31	1	122
	31	2	591
NF Monographs			
Acesulfame Potassium—*Packaging and storage* (add)	31	1	87
Acetyltributyl Citrate—*Assay*	30	6	2078
Acetyltriethyl Citrate—*Assay*	30	6	2079
Adipic Acid—*Packaging and storage* (add), *USP Reference standards* (add)	31	1	87
Alfadex—*Packaging and storage*	30	1	202
Ammonio Methacrylate Copolymer—*Identification B*	30	5	1666
Ammonio Methacrylate Copolymer Dispersion—*Identification A, B*	31	2	483
Asparagine—*Packaging and storage* (add), *USP Reference standards, Identification, Chromatographic purity*	31	1	87
Purified Bentonite—*Assay for aluminum and magnesium content*	31	2	483
Butylparaben (new) [Harmonization]	31	1	191
Calcium Silicate—*Definition, pH, Limit of fluoride, Assay of silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	30	2	595
Carbomer 934—*Labeling*	31	2	484
Carbomer 934 P—*Labeling* (add), *Limit of benzene*	31	2	484
Carbomer 940—*Labeling, Viscosity*	31	2	485
Carbomer 941—*Labeling*	31	2	485
Carbomer 1342—*Labeling*	31	2	485
Carbomer Copolymer—*Definition, Labeling, Limit of benzene* (add), *Organic volatile impurities* (add), *Content of carboxylic acid*	31	2	486

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Carbomer Homopolymer (new)	31	2	488
Carbomer Interpolymer—*Labeling, Limit of benzene* (add), *Organic volatile impurities* (add)	31	2	493
Cellaburate—*Packaging and storage*	30	3	967
Cetostearyl Alcohol—*Assay*	31	2	494
Cetyl Alcohol—*Assay*	31	2	494
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Croscarmellose Sodium [Harmonization]—*Residue on ignition*	30	4	1439
Crospovidone—*Monograph*	28	4	1257
Ferric Oxide—*Acid-insoluble substances*	31	1	88
Galactose—*Packaging and storage* (add)	31	1	88
Glyceryl Monostearate—*USP Reference standards* (delete), *Hydroxyl value, Saponification value, Assay for monoglycerides*	31	2	495
Purified Honey (new)	31	2	496
Hydroxyethyl Cellulose (new) [Harmonization]	30	2	709
Low-Substituted Hydroxypropyl Cellulose [Harmonization]	30	1	338
Hypromellose Acetate Succinate (new)	30	6	2079
Isomalt (new)	31	1	88
Lauroyl Macrogoglycerides (new)	28	4	1212
Lauroyl Polyoxylglycerides (new)	31	1	92
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate [Harmonization]	30	1	340
Maltol—*Packaging and storage*	30	3	984
Methacrylic Acid Copolymer—*Limit of monomers*	31	1	93
Monoglyceride Citrate (new)	30	6	2088
Myristic Acid (new)	30	5	1666
Neotame (new)	31	2	497
Nitrogen—*Assay*	28	4	1219
Nitrogen 97 Percent—*Assay*	28	4	1220
Phenolsulfonphthalein—*Labeling* (add), *USP Reference standards* (add), *Bacterial endotoxins* (add)	31	1	94
Polyethylene Glycol [Harmonization]	28	2	577
Polyethylene Oxide—*Organic volatile impurities*	31	1	95
Polyisobutylene—*Definition, Labeling, Molecular weight* (delete), *Viscosity* (add)	30	6	2089
Polydecene (new)	30	4	1331
Polyoxyl 35 Castor Oil—*USP Reference standards* (add), *Identification A*	30	5	1668

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Propylene Glycol Dilaurate (new)	31	2	500
Propylene Glycol Monolaurate (new)	31	2	501
Propylparaben [Harmonization]—*Packaging and storage*	30	4	1448
Saccharin	31	2	616
Saccharin (new) [Harmonization]	31	2	618
Sesame Oil—*Definition, Labeling* (not NL issue), *USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Sodium Caprylate—*Packaging and storage*	30	3	990
Sodium Starch Glycolate [Harmonization]	30	4	1455
Sodium Tartrate—*Packaging and storage*	31	1	95
Sorbitol Sorbitan Solution (Anhydrized Liquid Sorbitol) (new)	30	5	1669
Corn Starch—*Packaging and storage* (add)	30	5	1862
Potato Starch—*Packaging and storage (add)*	30	5	1865
Rice Starch (new) [Harmonization]	30	2	721
Tapioca Starch—*Iron*	30	5	1672
Wheat Starch—*Packaging and storage* (add)	30	5	1868
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Succinic Acid—*Packaging and storage*	31	1	95
Sunflower Oil (new)	31	1	95
Tagatose (new)	30	5	1672
Tributyl Citrate—*Assay*	30	6	2091
Triethyl Citrate—*Assay*	30	6	2091
Medium-Chain Triglycerides—*Definition*	31	1	98

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USP Monographs			
†Acepromazine Maleate—*Labeling, Other requirements*	29	6	1832
†Acyclovir—*Labeling, USP Reference standards, Other requirements*	30	5	1580
†Adenosine—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Albendazole Oral Suspension—*Labeling*	29	4	991
†Albuterol Tablets—*Assay*	31	1	40
Alcohol—*Harmonization*	30	2	670
Dehydrated Alcohol—*Harmonization*	30	2	673
†Alfentanil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1834
†Alprostadil—*Labeling, USP Reference standards, Other requirements*	29	5	1412
†Alteplase—*Labeling, Other requirements*	29	6	1835
†Amifostine—*Labeling, USP Reference standards, Other requirements, Assay*	30	6	1974
†Aminocaproic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1414
†Aminopentamide Sulfate—*Labeling, USP Reference standards, Other requirements*	30	4	1163
†Aminophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1414
†Amitriptyline Hydrochloride—*Labeling, Other requirements*	29	6	1844
†Ammonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1415
†Ammonium Molybdate—*Labeling, Other requirements*	29	5	1416
†Amphotericin B Lotion—*Title*	30	2	444
†Amphotericin B Topical Emulsion (entire submission)	30	2	445
†Anileridine—*Labeling, USP Reference standards, Other requirements*	29	6	1846
†Atenolol—*Labeling, USP Reference standards, Other requirements*	29	5	1416
†Atracurium Besylate—*Labeling, USP Reference standards, Other requirements*	29	6	1846
†Atropine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1847
†Aurothioglucose—*Labeling, Other requirements*	29	6	1847
†Azaperone—*Labeling, Other requirements*	29	6	1847
†Benzoyl Peroxide Lotion—*Title*	30	2	456
†Benzoyl Peroxide Topical Emulsion (entire submission)	30	2	456
†Benztropine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1848
†Benzyl Benzoate Lotion—*Title*	30	2	457
†Benzyl Benzoate Topical Emulsion (entire submission)	30	2	457
†Betamethasone Tablets—*Identification, Thin-layer chromatographic identification test*	30	1	62
†Betamethasone Dipropionate Lotion—*Title*	30	2	458
†Betamethasone Dipropionate Topical Emulsion (entire submission)	30	2	459
†Betamethasone Valerate Lotion—*Title*	30	2	461
†Betamethasone Valerate Topical Emulsion (entire submission)	30	2	461
†Bethanechol Chloride—*Labeling, USP Reference standards, Other requirements*	30	5	1586
†Biperiden—*Labeling, USP Reference standards, Other requirements*	29	6	1851
†Bretylium Tosylate—*Labeling, USP Reference standards, Other requirements*	29	5	1431

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†Brompheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1431
†Bumetanide—*Labeling, USP Reference standards, Other requirements*	29	5	1432
†Bupivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	5	1589
†Butorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1851
†Caffeine—*Labeling, USP Reference standards, Other requirements*	30	4	1168
†Calcium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1436
†Carboprost Tromethamine—*Labeling, USP Reference standards, Other requirements*	30	1	82
Carboxymethylcellulose Sodium—*Harmonization*	28	3	867
†Chlordiazepoxide Hydrochloride—*USP Reference standards*	29	6	1859
†Chloroprocaine Hydrochloride—*Labeling, Other requirements*	29	5	1438
†Chloroquine—*Labeling, USP Reference standards, Other requirements*	29	6	1859
†Chlorothiazide—*Labeling, USP Reference standards, Other requirements*	29	5	1439
†Chlorpheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1439
†Chlorpromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1860
†Chromic Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1440
†Cimetidine—*Labeling, USP Reference standards, Other requirements*	29	5	1440
†Ciprofloxacin Hydrochloride—*Labeling, Other requirements*	29	6	1861
Clonidine Hydrochloride Injection (new)—*Preview*	26	2	351
†Clotrimazole Lotion—*Title*	30	2	473
†Clotrimazole Topical Emulsion (entire submission)	30	2	474
†Codeine Phosphate—*Labeling, USP Reference standards, Other requirements*	30	5	1597
†Cortisone Acetate—*Labeling, Other requirements*	29	5	1447
†Cupric Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1864
†Cupric Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1447
†Deslanoside—*Labeling, Other requirements*	29	5	1448
Desmopressin Acetate (new)—*Preview*	24	2	5773
Desmopressin Injection (new)—*Preview*	24	2	5778
Desmopressin Nasal Spray Solution (new)—*Preview*	24	2	5779
†Desoxycorticosterone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1456
†Desoxycorticosterone Pivalate—*Labeling, USP Reference standards, Other requirements*	29	6	1865
†Dexamethasone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1457
†Dextran 1—*Other requirements*	29	6	1866
†Dextran 40—*Other requirements*	29	6	1866
†Dextran 70—*Other requirements*	29	6	1868
†Dextrose—*Labeling, USP Reference standards, Other requirements*	29	5	1457
†Diatrizoate Meglumine—*Labeling, USP Reference standards, Other requirements*	30	3	832
†Diatrizoate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1868

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†Diatrizoic Acid—*Labeling, USP Reference standards, Other requirements*	29	6	1869
†Diazepam—*Labeling, USP Reference standards, Other requirements*	30	1	96
†Diazoxide—*Labeling, USP Reference standards, Other requirements*	29	5	1458
†Dibucaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
†Dicyclomine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
†Diethylstilbestrol—*Labeling, USP Reference standards, Other requirements*	29	5	1463
†Diethylstilbestrol Diphosphate Tablets (entire submission)	30	4	1187
†Dihydroergotamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1870
†Dimenhydrinate—*Labeling, Other requirements*	29	5	1466
†Dimercaprol—*Labeling, Other requirements*	29	5	1466
†Diphenhydramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1466
†Dipyridamole—*Labeling, USP Reference standards, Other requirements*	29	5	1467
†Dobutamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1467
†Dolasetron Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1468
†Dopamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1469
†Doxapram Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1874
Doxycycline Hyclate—*Content of ethanol*	30	3	836
†Droperidol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1875
†Dyphylline—*Labeling, USP Reference standards, Other requirements*	29	5	1473
†Edetate Calcium Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
†Edetate Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
†Edrophonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1475
†Emetine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1875
†Ephedrine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	3	840
†Epinephrine—*Labeling, USP Reference standards, Other requirements*	29	5	1476
†Ergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1478
†Ergotamine Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1884
†Estradiol—*Labeling, USP Reference standards, Other requirements*	29	5	1478
†Estrone—*Labeling, USP Reference standards, Other requirements*	29	5	1479
†Ethacrynic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1479
†Fenoldopam Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1479
†Fentanyl Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1885
†Flunixin Meglumine—*Labeling, USP Reference standards, Other requirements*	29	6	1886

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Fluoxetine Hydrochloride—*USP Reference standards, Related compounds*	30	3	848
†Fluphenazine Decanoate—*Labeling, USP Reference standards, Other requirements*	29	6	1887
†Fluphenazine Enanthate—*Labeling, USP Reference standards, Other requirements*	29	6	1887
†Fluphenazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1888
†Flurandrenolide Lotion—*Title*	30	2	489
†Flurandrenolide Topical Emulsion (entire submission)	30	2	489
†Fosphenytoin Sodium—*Labeling, Other requirements*	29	6	1888
†Fructose—*Labeling, USP Reference standards, Other requirements*	29	5	1496
†Furosemide—*Labeling, USP Reference standards, Other requirements*	29	5	1497
Gabapentin (entire submission)	29	1	72
†Gadodiamide—*Labeling, Other requirements*	29	6	1889
†Gadoteridol—*Labeling, USP Reference standards*	29	6	1890
†Gallamine Triethiodide—*Labeling, USP Reference standards, Other requirements*	29	5	1503
†Ganciclovir—*Labeling, USP Reference standards, Other requirements*	29	6	1890
†Glucagon—*Labeling, USP Reference standards, Other requirements*	30	5	1625
†Glycerin—*Labeling, Other requirements*	29	6	1895
†Glycopyrrolate—*Labeling, USP Reference standards, Other requirements*	29	5	1503
†Gold Sodium Thiomalate—*Labeling, Other requirements*	29	6	1895
†Chorionic Gonadotropin—*Labeling*	29	6	1896
†Haloperidol—*Labeling, USP Reference standards, Other requirements*	29	6	1897
†Histamine Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1504
†Hydralazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1505
†Hydrocortisone—*Labeling, USP Reference standards, Other requirements*	29	5	1506
†Hydrocortisone Lotion—*Title*	30	2	505
†Hydrocortisone Topical Emulsion (entire submission)	30	2	506
†Hydrocortisone Acetate Lotion—*Title*	30	2	504
†Hydrocortisone Acetate Ointment—*Assay*	30	2	504
†Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	504
†Hydromorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	4	1254
†Hydroxyprogesterone Caproate—*Labeling, Other requirements*	29	5	1506
†Hydroxyzine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1902
†Hyoscyamine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1507
†Imipramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1904
†Inamrinone—*Labeling, USP Reference standards, Other requirements*	29	5	1507
†Indigotindisulfonate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1905
†Insulin—*Labeling, Other requirements, Limit of high molecular weight proteins*	30	5	1629
†Insulin Human—*Labeling, Other requirements*	29	6	1906
†Inulin—*Labeling, USP Reference standards, Other requirements*	29	6	1906

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†Iodipamide—*Labeling, USP Reference standards, Other requirements*	29	6	1907
†Iodixanol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1908
†Iohexol—*Labeling, USP Reference standards, Other requirements*	29	6	1908
†Iopamidol—*Labeling, USP Reference standards, Other requirements*	29	6	1909
†Iophendylate—*Labeling, USP Reference standards, Other requirements*	29	6	1910
†Iothalamic Acid—*Labeling, USP Reference standards, Other requirements*	29	6	1910
†Ioversol—*Labeling, USP Reference standards, Other requirements*	29	6	1910
†Ioxaglic Acid—*Labeling, Other requirements*	29	6	1911
†Ioxilan—*Labeling, Other requirements*	29	6	1911
†Isoniazid—*Labeling, USP Reference standards, Other requirements*	29	6	1912
†Isoproterenol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1509
†Ketamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1913
†Ketorolac Tromethamine—*Labeling, USP Reference standards, Other requirements*	29	6	1915
†Labetalol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Leuprolide Acetate Injection (new)—*Preview*	25	5	8722
†Levorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1916
†Levothyroxine Sodium Tablets—*Test 3*	29	3	634
†Lidocaine Hydrochloride—*Assay*	30	4	1256
†Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	30	4	1257
†Lindane Lotion—*Title*	30	2	512
†Lindane Topical Emulsion (entire submission)	30	2	512
†Lorazepam—*Labeling, USP Reference standards, Other requirements*	29	6	1918
†Magnesium Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1921
†Malathion Lotion—*Title*	30	2	513
†Malathion Topical Emulsion (entire submission)	30	2	513
†Mangafodipir Trisodium—*Labeling, Other requirements*	30	6	2014
†Manganese Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1526
†Manganese Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1922
†Mannitol (entire submission)	27	5	3017
†Mannitol Injection (entire submission)	27	5	3020
†Mebrofenin—*Labeling, USP Reference standards, Other requirements*	29	6	1923
†Medroxyprogesterone Acetate—*Labeling, Other requirements*	29	5	1526
†Menadiol Sodium Diphosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1531
†Menadione—*Labeling, USP Reference standards, Other requirements*	29	5	1531
†Menotropins—*Labeling, Other requirements*	29	6	1923
†Meperidine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1924
†Mepivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1533

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* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†Mesoridazine Besylate—*Labeling, USP Reference standards, Other requirements*	30	4	1262
†Metaraminol Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1533
†Methadone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1929
†Methocarbamol—*Labeling, USP Reference standards, Other requirements*	29	6	1930
†Methohexital—*Labeling, USP Reference standards, Other requirements*	29	5	1534
†Methotrimeprazine—*Labeling, USP Reference standards, Other requirements*	29	6	1931
†Methylbenzethonium Chloride Lotion—*Title*	30	2	515
†Methylbenzethonium Chloride Topical Emulsion (entire submission)	30	2	515
†Methylbenzethonium Chloride Topical Powder—*Assay*	30	2	516
†Methyldopate Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1534
†Methylene Blue—*Labeling, USP Reference standards, Other requirements*	29	5	1534
†Methylergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1535
†Methylprednisolone Acetate—*Labeling, Other requirements*	29	5	1535
†Metoclopramide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1536
†Metoprolol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1536
†Metronidazole—*Labeling, USP Reference standards, Other requirements*	29	6	1933
†Miconazole—*Labeling, USP Reference standards, Other requirements*	29	6	1934
†Morphine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	5	1639
†Nalorphine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1935
†Naloxone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1936
†Nandrolone Decanoate—*Labeling, Other requirements*	29	5	1539
†Neomycin Sulfate and Flurandrenolide Lotion—*Title*	30	2	516
†Neomycin Sulfate and Flurandrenolide Topical Emulsion (entire submission)	30	2	516
†Neomycin Sulfate and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	517
†Neomycin Sulfate and Hydrocortisone Acetate Lotion—*Title*	30	2	517
†Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	518
†Neomycin Sulfate and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	518
†Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	518
†Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	519
†Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519
†Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519

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(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
	Vol.	*No.*	*Page(s)*
†Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
†Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
†Neostigmine Methylsulfate—*Labeling, Other requirements*	29	6	1936
†Diluted Nitroglycerin—*Labeling, USP Reference standards, Other requirements*	29	5	1547
†Norepinephrine Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1547
†Nystatin Lotion—*Title*	30	2	522
†Nystatin Topical Emulsion (entire submission)	30	2	522
†Ofloxacin—*Labeling, USP Reference standards, Other requirements*	30	4	1274
†Ondansetron Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1941
†Orphenadrine Citrate—*Labeling, USP Reference standards, Other requirements*	30	2	523
†Oxandrolone—*Definition, Identification B, Ordinary impurities, Related compounds, Assay*	30	1	148
†Oxymorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1946
†Oxytocin—*Labeling, USP Reference standards, Other requirements*	29	6	1946
†Paclitaxel—*USP Reference standards, Related compounds (C)*	30	4	1279
†Padimate O Lotion—*Title*	30	2	527
†Padimate O Topical Emulsion (entire submission)	30	2	527
†Papaverine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1551
†Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension—*Assay for hydrocortisone acetate*	30	2	528
†Pentobarbital—*Labeling, USP Reference standards, Other requirements*	30	1	154
†Pentobarbital Sodium—*Labeling, USP Reference standards, Other requirements*	30	1	157
†Perphenazine—*Labeling, USP Reference standards, Other requirements*	29	6	1963
†Phenobarbital—*Labeling, USP Reference standards, Other requirements*	29	6	1964
†Phentolamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1562
†Phenylbutazone Injection—*USP Reference standards*	29	6	1964
†Phenylephrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1964
†Phenytoin Sodium—*Labeling, USP Reference standards, Other requirements*	30	6	2030
†Physostigmine Salicylate—*Labeling, USP Reference standards, Other requirements*	29	6	1967
†Potassium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1562
†Dibasic Potassium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1563
†Prednisolone Acetate—*Labeling, Other requirements*	30	5	1642
†Prilocaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1564
†Procainamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1565
†Prochlorperazine Edisylate—*Labeling, USP Reference standards, Other requirements*	29	5	1565
†Progesterone—*Labeling, Other requirements*	29	5	1566

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[*PF* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†Promazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1566
†Promethazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1567
†Propoxycaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	6	2032
†Propranolol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1568
†Propyliodone—*Labeling, Other requirements*	29	6	1976
†Pyridostigmine Bromide—*Labeling, USP Reference standards, Other requirements*	29	6	1977
†Quinidine Gluconate—*Labeling, USP Reference standards, Other requirements*	29	5	1568
†Ranitidine Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	28	2	360
†Reserpine—*Labeling, USP Reference standards, Other requirements*	29	5	1570
†Ritodrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1570
†Selenious Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1571
†Sodium Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1576
†Sodium Bicarbonate—*Labeling, USP Reference standards, Other requirements*	29	5	1577
†Sodium Nitrite—*Labeling, USP Reference standards, Other requirements*	29	5	1577
†Dibasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1578
†Monobasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
†Sodium Sulfate—*Labeling, Other requirements*	29	5	1579
†Sodium Thiosulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
†Sufentanil Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1988
†Sulfadiazine Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1988
†Sulfamethoxazole—*Labeling, Other requirements*	29	6	1989
†Terbutaline Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Terbutaline Sulfate Inhalation Aerosol (entire submission)	26	3	753
†Terbutaline Sulfate Injection—*USP Reference standards, Identification, Assay*	26	3	756
†Testosterone—*Labeling, USP Reference standards, Other requirements*	29	5	1585
†Theophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1586
†Thiopental Sodium—*Labeling, USP Reference standards, Other requirements*	29	5	1586
†Thiothixene Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
†Tolazoline Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1588
†Triamcinolone Acetonide—*Labeling, USP Reference standards, Other requirements*	30	3	945
†Triamcinolone Acetonide Lotion—*Title*	30	2	538
†Triamcinolone Acetonide Topical Emulsion (entire submission)	30	2	538

In-Process Revision

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[*PF* 31(1)–*PF* 31(6)] *(Continued)*

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†Trifluoperazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
†Triflupromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1994
†Trimethobenzamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1589
†Trimethoprim—*Labeling, Other requirements*	29	6	1995
†Trimethoprim Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1995
†Tubocurarine Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1996
†Urofollitropin (new) (entire submission)	28	6	1875
†Urofollitropin for Injection (new) (entire submission)	28	6	1881
Valproic Acid Injection (new)—*Preview*	26	4	939
†Vasopressin—*Labeling, USP Reference standards, Other requirements*	29	6	2004
†Verapamil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1598
†Xylazine—*Labeling, USP Reference standards, Other requirements*	29	6	2004
†Xylazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
†Yohimbine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
†Zidovudine—*Labeling, USP Reference standards, Other requirements*	29	6	2006
Dietary Supplements Monographs			
†Fish Oil Rich in Omega-3 Acids (new) (entire submission)	29	4	1272
†Fish Oil Rich in Omega-3 Acids Capsules (new) (entire submission)	29	4	1278
Shark Liver Oil (new)—*Preview*	26	6	1643
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
†*USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS*	30	6	2092
USP Fluoxetine Related Compound B Solution RS	30	4	1338
†*USP Paclitaxel Related Compound C RS*	30	4	1338
†*USP Phenylephrine Bitartrate RS*	30	3	998
USP Tazobactam Sodium RS	29	3	711
⟨601⟩ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers—*Harmonization*	28	2	584
⟨621⟩ Chromatography—*Chromatographic Reagents, Phases* (Docosahexaenoic Acid)	29	6	2023
†⟨643⟩ Total Organic Carbon (entire submission)	30	5	1700
†⟨701⟩ Disintegration—*Harmonization*	28	5	1575
†⟨711⟩ Dissolution—*Harmonization*	28	6	1981
⟨776⟩ Optical Microscopy—*Harmonization*	28	2	606
⟨786⟩ Particle Size Distribution by Analytical Sieving—*Harmonization*	28	5	1581
⟨811⟩ Powder Fineness (entire submission)	28	2	611
†⟨943⟩ X-Ray Diffraction—Solids (new) (entire submission)	28	3	905
USP General Information Chapters			
⟨1174⟩ Powder Flow (new)—*Harmonization*	28	2	618
⟨1198⟩ Standardized Imprint Codes for Solid Oral Dosage Forms (new)—*Preview*	28	1	152
⟨1225⟩ Validation of Compendial Methods—*Validation—Ruggedness*	30	4	1382
Reagents, Indicators, and Solutions			
†4-Chlorophenol (added)	30	3	1045
Dioleoylglycerol (added)—*Preview*	26	6	1622

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[*PF* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Monooleoylglycerol (added)—*Preview*	26	6	1622
Pentadecanoic Acid Methyl Ester (added)—*Preview*	26	6	1622
1,1,4,4-Tetraphenyl-1,3-butadiene (added)	26	6	1623
Trioleoylglycerol (added)—*Preview*	26	6	1623
Reference Tables			
Container Specifications			
†Diethylstilbestrol Diphosphate Tablets	30	4	1404
NF Monographs			
Adipic Acid—*Packaging and storage*	30	4	1322
†Microcrystalline Cellulose *(Harmonization)—Packaging and storage*	30	4	1435
†Powdered Cellulose *(Harmonization)—Packaging and storage*	30	4	1438
Docosahexaenoic Acid (new)—*Preview*	26	6	1648
Docosahexaenoic Acid Capsules (new)—*Preview*	26	6	1651
Docosahexaenoic Acid Oil (new)—*Preview*	26	6	1652
†Ethylparaben *(Harmonization)—Packaging and storage*	30	4	1444
Medium-Chain Triglycerides—*Packaging and storage*	30	3	998
†Methylparaben *(Harmonization)—Packaging and storage*	30	4	1446
†Phenoxyethanol—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94

†New cancellations in *PF* 31(3).

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

Polyethylene Glycol, *NF 23* page 3053 and page 1313 of *PF* 29(4) [July–Aug. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Polyethylene Glycol* 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 Revised **OFFICIAL INQUIRY STAGE 4** document, is based in part on comments from the European and Japanese Pharmacopoeias in response to the Harmonization Stage 4 draft prepared by the United States Pharmacopeia.

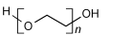
Differences between the Revised **OFFICIAL INQUIRY STAGE 4** document and the current *NF* monograph include the following:

(1) Opening paragraph (Definition)—The limits for the average molecular weight have been omitted from the monograph. Those limits were considered redundant, because viscosity is tested and limited.
(2) *Packaging and storage*—"Well-closed containers" has been changed to "tight containers" because of the potential volatility of some lower molecular weight polyethylene glycols that are in liquid form.
(3) *Labeling*—No change.
(4) *USP Reference standards*—New Reference Standards are added to comply with the proposed *Infrared Absorption* test in *Identification.*
(5) *Completeness and color of solution*—The test is modified to use color comparison standards.
(6) *Identification*—A new, definitive *Identification* test, test *A,* based on IR spectroscopy performed by comparison with a Reference Standard, is added. The test for *Viscosity* is referenced in the *Identification* section, because that test can be used to distinguish between the various grades of material.
(7) *Viscosity*—The EP method for the *Viscosity* test is adopted, because it is easier to perform than the *USP* test and complies with the molecular weight range of 200 to 35,000.
(8) *Average molecular weight*—This test is omitted on the basis of the viscosity–molecular weight relationship among the polyethylene glycols. Polytheylene glycols are typically employed on the basis of their viscosity.
(9) *pH*—The limit is changed from between 4.5 and 7.5 to between 4.0 and 7.5.
(10) *Water*—A new test for *Water* is added, with a limit corresponding to that in the JP monograph.
(11) *Residue on ignition*—The sample weight has been lowered to 2.00 g, and the use of a platinum dish is omitted because it is not necessary.
(12) *Heavy metals*—This test is omitted, because Polyethylene Glycol is totally organic and not derived from any materials that usually contain heavy metals.
(13) *Limit of ethylene oxide and dioxane*—The test is modified to use a readily available ethylene oxide standard. The limit for ethylene oxide is lowered from not more than 10 µg per g to not more than 1 µg per g.
(14) *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* are added. The limit is changed to not more than 620 ppm for ethylene glycol to comply with currrent *International Conference on Harmonization* (ICH) guidelines.
(15) *Limit of formaldehyde*—This test is added to limit cross-linking when Polythylene Glycol is used with gelatin capsules.
(16) *Organic volatile impurities*—This test is omitted, because it is unnecessary for this compound.

(EMC: J. Lane) RTS—42266-1

Add the following:

Polyethylene Glycol



Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-.

Polyethylene glycol [*25322-68-3*].

» 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 nominal average molecular weight is from 200 to 35,000. It may contain a suitable antioxidant.

Packaging and storage—Preserve in tight containers, protected from direct sunlight.

Labeling—Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol. Label it to indicate the name and quantity of any added antioxidant.

USP Reference standards ⟨11⟩—*USP Polyethylene Glycol 200 RS. USP Polyethylene Glycol 300 RS. USP Polyethylene Glycol 400 RS. USP Polyethylene Glycol 600 RS. USP Polyethylene Glycol 1000 RS. USP Polyethylene Glycol 1500 RS. USP Polyethylene Glycol 3000 RS. USP Polyethylene Glycol 3350 RS. USP Polyethylene Glycol 4000 RS. USP Polyethylene Glycol 6000 RS. USP Polyethylene Glycol 8000 RS. USP Polyethylene Glycol 10000 RS. USP Polyethylene Glycol 12000 RS. USP Polyethylene Glycol 20000 RS. USP Polyethylene Glycol 35000 RS.*

Completeness and color of solution—

Standard stock solution—Combine 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, 0.4 mL of cupric sulfate CS, and 6.2 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 5.0 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 A—Dissolve 12.5 g of Polyethylene Glycol in water, and dilute with water to 50 mL.

Test solution B—Dissolve 5.0 g of Polyethylene Glycol in water, and dilute with water to 50 mL.

Procedure—Separately transfer a sufficient portion of *Test solution A* and *Test solution B* 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 *Standard solution* to a separate matching test tube. Compare the test material and the *Standard solution* in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). *Test solution A* is not more intensely colored than the *Standard solution*. *Test solution B* has the same clarity as that of water, when viewed against a black background, at 25 ± 5°, for nominal average molecular weights less than or equal to 1000, and is not more than slightly hazy for nominal average molecular weights greater than 1000.

Identification—

A: *Infrared Absorption* ⟨197K⟩—Use a thin film of test specimen, melted if necessary, in the range from 4000 cm^{-1} to 600 cm^{-1}.

B: It meets the requirements of the test for *Viscosity.*

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 20 ± 0.1°. For polyethylene glycols having a nominal average molecular weight greater than 400, determine the viscosity of 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

Nominal Average Molecular Weight	Kinematic Viscosity Range, Centistokes ($mm^2 \cdot s^{-1}$)
12,000	1000–1300
20,000	2500–3200
35,000	10,000–13,000

pH ⟨791⟩**—**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.

Water ⟨921⟩**:** not more than 1.0%, determined on 2.00 g.

Residue on ignition ⟨281⟩**:** not more than 0.1%, a 2-g specimen and the residue being moistened with 2 mL of sulfuric acid.

Limit of ethylene oxide and dioxane—

Ethylene oxide standard solution—Dilute 0.5 mL of ethylene oxide in methylene chloride (50 mg per mL) with water to 50.0 mL. [NOTE—The solution is stable for 3 months if stored in vials with teflon-coated silicon membrane crimped caps at –20°.] Allow to reach room temperature. Dilute 1.0 mL of this solution with water to 250.0 mL to obtain a solution having a concentration of 2 µg per mL.

Dioxane standard solution—Dilute 1.0 mL of dioxane with water to 200.0 mL. Dilute 1.0 mL of this solution with water to 100.0 mL to obtain a solution having a concentration of 50 µg per mL.

Acetaldehyde standard solution—Accurately weigh about 100 mg of acetaldehyde into a 100-mL volumetric flask, and dilute with water to volume. Transfer 1.0 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume to obtain a solution having a concentration of 10 µg per mL.

Resolution solution—Add 2.0 mL of *Acetaldehyde standard solution* and 2.0 mL of *Ethylene oxide standard solution* to a 10-mL headspace vial, and seal the vial immediately with a teflon-coated silicon membrane and an aluminum cap. Mix carefully.

Standard solution A—Dilute 6.0 mL of *Ethylene oxide standard solution* and 2.5 mL of *Dioxane standard solution* with water to 25.0 mL.

Standard solution B—Accurately weigh 1.00 g of the substance to be examined into a 10-mL headspace vial. Add 2.0 mL of *Standard solution A,* and seal the vial immediately with a teflon-coated silicon membrane and an aluminum cap. Mix carefully.

Test solution—Accurately weigh 1.00 g of the substance to be examined into a 10-mL headspace vial. Add 2.0 mL of water, and seal the vial immediately with a teflon-coated silicon membrane and an aluminum cap. Mix carefully.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a balanced-pressure automatic headspace sampler, a flame-ionization detector, a split injection system, and a 0.32-mm × 50-m fused-silica analytical column coated with a 5-µm film of phase G27. The carrier gas is helium, with a column pressure of about 70 kPa, and a total flow of about 20 mL per minute. The column temperature is increased from 70° to 250° at a rate of 10° per minute, then maintained at 250° for at least 5 minutes. The injection port and detector temperatures are maintained at 85° and 250°, respectively. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 0.9 for acetaldehyde and 1.0 for ethylene oxide; and the resolution, *R,* between acetaldehyde and ethylene oxide is not less than 2.0.

Procedure—Place the vials containing *Standard solution B* and the *Test solution* into the automated sampler, and heat the vials at a temperature of 80° for 30 minutes. Using a 2-mL gas syringe preheated in an oven at 90°, separately inject 1.0 mL of the headspace from each vial into the chromatograph, record the chromatogram, and measure the areas for the major peaks. [NOTE—A headspace apparatus that automatically transfers the measured amount of headspace may be used to perform the injection.] The relative retention times for ethylene oxide and dioxane are about 1.0 and 1.8, respectively. Calculate the amount, in µg per g, of ethylene oxide in the portion of Polyethylene Glycol taken by the formula:

$$2Cr_U/(r_S - r_U),$$

in which C is the concentration, in µg per mL, of ethylene oxide in *Standard solution B;* and r_U and r_S are the peak areas of ethylene oxide obtained from the *Test solution* and *Standard solution B*, respectively: not more than 1 µg per g of ethylene oxide is found. Calculate the amount, in µg per g, of dioxane in the portion of Polyethylene Glycol taken by the formula:

$$[2(1.03)Cr_U]/(r_S - r_U),$$

in which C is the concentration, in µL per mL, of dioxane in *Standard solution B;* 1.03 is the density of dioxane, in g per mL; and r_U and r_S are the peak areas of dioxane obtained from the *Test solution* and *Standard solution B*, respectively: not more than 10 µg per g of dioxane is found.

Limit of ethylene glycol and diethylene glycol—

NOTE—Testing is not required for nominal average molecular weights greater than 1000.

Internal standard solution—Dissolve 30.0 mg of 1,2-pentanediol, accurately weighed, in acetone, and dilute with the same solvent to 30.0 mL. Dilute 1.0 mL of this solution with acetone to 20.0 mL to obtain a solution having a concentration of 50 µg per mL.

Standard solution A—Dissolve 30.0 mg of ethylene glycol, accurately weighed, in acetone, and dilute with the same solvent to 100.0 mL. Dilute 1.0 mL of this solution with the *Internal standard solution* to 10.0 mL to obtain a solution having a concentration of 30 µg per mL of ethylene glycol and 45 µg per mL of 1-2-pentanediol.

Standard solution B—Dissolve 200.0 mg of diethylene glycol, accurately weighed, in acetone, and dilute with the same solvent to 100.0 mL. Dilute 1.0 mL of this solution with the *Internal standard solution* to 10.0 mL to obtain a solution having a concentration of 200 µg per mL of ethylene glycol and 45 µg per mL of 1,2-pentanediol.

Test solution—Transfer about 500 mg of Polyethylene Glycol, accurately weighed, to a 10-mL volumetric flask, and dissolve in and dilute with *Internal standard solution* to volume to obtain a solution having a concentration of 50 µg per mL of 1,2-pentanediol.

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-µm film of phase G16. The carrier gas is helium, flowing at a rate of about 30 mL per minute, and the split ratio is about 1 : 3. The column temperature is programmed to increase from 80° to 200° from the time of injection to 40 minutes, and from 200° to 230° from 40 minutes to 45 minutes; then it is maintained at 230° for at least 20 minutes. The injection port and detector temperatures are maintained at 250°. Chromatograph *Standard solution A,* and record the peak responses as directed for *Procedure*: the relative retention times are

about 0.7 for ethylene glycol, about 1.0 for 1,2-pentanediol, and about 1.3 for diethylene glycol; the resolution, *R,* between ethylene glycol and 1,2-pentanediol is not less than 2.0; and the resolution, *R,* between the 1,2-pentanediol and diethylene glycol is not less than 2.0.

Procedure—Inject 2 µL of *Standard solution A* and 2 µL of *Standard solution B* into the chromatograph, record the chromatogram, and measure the areas of the peaks for ethylene glycol, the internal standard, and diethylene glycol, recorded as r_{SE}, r_{SI}, and r_{SD}, respectively. Inject 2 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas as directed for *Standard solution A* and *Standard solution B*. Use the retention times observed in the chromatogram of *Standard solutions A* and *B* 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 peaks for ethylene glycol, the internal standard, and diethylene glycol 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:

$$(F_N C_I\, r_N) / (r_I W),$$

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 mg, of Polyethylene Glycol taken to prepare the *Test solution:* not more than 620 ppm of ethylene glycol and not more than 0.2% of ethylene glycol and diethylene glycol combined are found.

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—Transfer 1.0 g of Polyethylene Glycol to a 10-mL volumetric flask, add about 3 mL of water, add 0.25 mL of *Chromotropic acid sodium solution,* and cool in iced water. Add 5.0 mL of sulfuric acid, allow to stand for 15 minutes, and dilute slowly with water to volume.

Reference solution—Dilute 0.860 g of formaldehyde solution with water to100 mL. Dilute 1.0 mL of this solution with water to 100 mL. In a 10-mL volumetric flask, mix 1.00 mL of this solution with 0.25 mL of *Chromotropic acid sodium solution.* Add 3.0 mL of water, cool in iced water, add 5.0 mL of sulfuric acid, allow to stand for 15 minutes, and dilute slowly with water to volume.

Blank solution—In a 10-mL volumetric flask mix 1.00 mL of water with 0.25 mL of *Chromotropic acid sodium solution,* and cool in iced water. Dilute slowly with water to volume.

Procedure—Determine against the *Blank solution* that the absorbance at 567 nm of the *Test solution* is not higher than that of the *Reference solution* (0.003%).

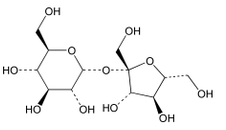
BRIEFING

Sucrose, *NF 23* page 3094. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Sucrose* 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 revised **OFFICIAL INQUIRY STAGE 4** document, is based in part on comments from the United States Pharmacopeia and Japanese Pharmacopoeia in response to the Harmonization Stage 4 draft prepared by the European Pharmacopoeia. The draft has been revised to introduce methods that are standards in the sugar industry and are approved by the International Commission for Uniform Methods in Sugar Analysis (ICUMSA). The current *USP* monograph contains tests for chloride, sulfate, calcium, and heavy metals, but these are considered unnecessary because the added test for *Conductivity* will effectively limit these ionic impurities. In addition to these changes, a *Bacterial endotoxins* test and a related *Labeling* requirement have been added.

(EMC: J. Lane) RTS—42289-1

Add the following:

Sucrose



$C_{12}H_{22}O_{11}$ 342.30

α-D-Glucopyranoside, β-D-fructofuranosyl-.

Sucrose [*57-50-1*].

» Sucrose is β-D-fructofuranosyl α-D-glycopyranoside. It contains no added substances.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to state, where applicable, that the substance is suitable for use in the manufacture of large-volume parenteral dosage forms.

Appearance of solution—Dissolve 50.0 g in water and dilute with the same solvent to 100.0 mL: the resulting solution is clear.

Color value—

Test solution—Dissolve 50.0 g in 50.0 mL of water. Mix, filter (diameter of pores 0.45 µm), and degas.

Procedure—Measure the absorbance at 420 nm, using a cell of at least 4 cm (a cell length of 10 cm or more is preferred). Calculate the color value using the expression:

$$(A \cdot 1000) / (b \cdot c),$$

in which A is the absorbance measured at 420 nm; b is the cell path length in centimeters; and c is the concentration of the solution, in g per mL, calculated from the refractive index of the solution. Use *Table 1,* and interpolate the values if necessary. The absolute difference between two results is not more than 3. The color value is not more than 45.

Table 1

n^{20}_D	c (g/mL)
1.4138	0.570
1.4159	0.585
1.4179	0.600
1.4200	0.615
1.4221	0.630
1.4243	0.645
1.4264	0.661

Identification, *Infrared Absorption* ⟨197K⟩.

Specific rotation ⟨781S⟩: +66.3° to +67.0°.

Test solution—Dissolve 26 g in water, and dilute with the same solvent to 100.0 mL.

Bacterial endotoxins ⟨85⟩**:** less than 0.25 IU per mg, if intended for use in the preparation of large-volume infusions.

Conductivity—

Test solution—Dissolve 31.3 g of Sucrose in freshly boiled and cooled water, and dilute with the same solvent to 100 mL.

Apparatus—Use a conductivity meter or resistivity meter that measures the resistance of the column of liquid between the electrodes of the immersed measuring device. The apparatus is supplied with alternating current to avoid the effects of electrode polarization. It is equipped with a temperature compensation device or a precision thermometer.

Calibration—Choose a conductivity cell that is appropriate for the conductivity of the solution to be examined. The higher the expected conductivity, the higher the cell constant that must be chosen so that the value measured, *R,* is as large as possible for the apparatus used. Commonly used conductivity cells have cell constants in the order of 0.1 cm^{-1}, 1 cm^{-1}, and 10 cm^{-1}. Use a standard solution of potassium chloride that is appropriate for the measurement. Rinse the cell several times with water that has been previously boiled and cooled to room temperature and at least twice with the potassium chloride solution used for the determination of the cell constant of the conductivity cell. Measure the resistance of the conductivity cell using the potassium chloride solution at $20 \pm 0.1^{\circ}$. The constant C (in cm^{-1}) of the conductivity cell is given by the expression:

$$C = R_{KCl} \times K_{KCl},$$

in which R_{KCl} is the measured resistance, expressed in megohms, and K_{KCl} is the conductivity of the standard solution of potassium chloride used, expressed in $\mu S \cdot cm^{-1}$. The measured constant, *C,* of the conductivity cell must be within 5% of the given value.

Procedure—Measure the conductivity of the *Test solution* (C_1), while gently stirring with a magnetic stirrer, and that of the water used for preparing the *Test solution* (C_2). The readings must be stable within 1% over a period of 30 seconds. Calculate the conductivity of the *Test solution* from the expression:

$$C_1 - 0.35C_2.$$

Not more than 35 $\mu S \cdot cm^{-1}$.

Loss on drying ⟨731⟩**:** not more than 0.1%, determined on 2.000 g by heating in an oven at 105° for 3 hours.

Dextrins—[NOTE—If intended for use in the preparation of large-volume infusions, it complies with the test for *Dextrins*.]

Test solution—Dissolve 50.0 g of Sucrose in water, and dilute with the same solvent to 100.0 mL.

Procedure—To 2 mL of the *Test solution* add 8 mL of water, 0.05 mL of dilute hydrochloric acid (73 g per L), and 0.05 mL of 0.05 M iodine. The solution remains yellow.

Sulfite—

Test solution—Dissolve 4.0 g of Sucrose in freshly prepared distilled water, and dilute with the same solvent to 10.0 mL.

Sulfite standard solution—Dissolve 3.150 g of anhydrous sodium sulfite in freshly prepared distilled water, and dilute with the same solvent to 100.0 mL. Dilute 0.5 mL of this solution with freshly prepared distilled water to 100.0 mL.

Reference solution—Dissolve 4.0 g of Sucrose in freshly prepared distilled water, add 0.5 mL of *Sulfite standard solution,* and dilute with freshly prepared distilled water to 10.0 mL. Use freshly prepared distilled water as the blank.

Procedure—Determine the sulfite content by a suitable enzymatic method based on the following reactions. Sulfite is oxidized by sulfite oxidase to sulphate and hydrogen peroxide, which in turn is reduced by nicotinamide–adenine di-

nucleotide–peroxidase in the presence of reduced nicotinamide–adenine dinucleotide (NADH). The amount of NADH oxidized is proportional to the amount of sulfite.

Separately introduce 2.0 mL each of the *Test solution,* the *Reference solution,* and the blank into 10-mm cuvettes, and add the reagents as described in the kit instructions. Measure the absorbance at the maximum at about 340 nm before and at the end of the reaction time and subtract the value obtained with the blank. The absorbance difference of the *Test solution* is not greater than half the absorbance difference of the *Reference solution:* not more than 10 ppm calculated as SO_2.

Lead—

Lead-free nitric acid: not more than 1 µg per kg of lead.

Dilute lead-free nitric acid—Dilute 5 g of *Lead-free nitric acid* with carbon dioxide-free water to 100 mL.

Test solution—Dissolve 1.5 g of Sucrose in 1.5 mL of carbon dioxide-free water in a digestion tube. Add 0.75 mL of *Lead-free nitric acid,* slowly warm to between 90° and 95°, and avoiding spattering. Heat for about 60 minutes, and again add 0.75 mL of *Lead-free nitric acid*. Heat until all brown vapors have dissipated and any reddish tint is gone (about 60 minutes). Cool. Add 0.5 mL of 30 percent hydrogen peroxide dropwise and heat at between 90° and 95° for 15 minutes. Cool. Again add 0.5 mL of 30 percent hydrogen peroxide dropwise, heat at between 90° and 95° for 60 minutes, and cool. Repeat these steps until a clear, light yellow solution is obtained. Dilute with carbon dioxide-free water to 10.0 mL. Store in capped plastic vials.

Lead standard solution (0.5 ppm Pb)—Dissolve in *Dilute lead-free nitric acid* a quantity of lead nitrate equivalent to 0.400 g of $Pb(NO_3)_2$, and dilute with the same solvent to 250 mL. Dilute with *Dilute lead-free nitric acid* to 100 times its volume. Dilute this solution with *Dilute lead-free nitric acid* to 20 times its volume. [NOTE—Use within 1 week.]

Reference solutions—Prepare three reference solutions in the same manner as the *Test solution* but adding 0.5 mL, 1.0 mL, and 1.5 mL, respectively, of *Lead standard solution (0.5 ppm Pb)* in addition to 1.5 g of Sucrose.

Blank solution—Prepare a blank in the same manner as for the *Test solution* but without Sucrose.

Zero-setting solution—Use carbon dioxide-free water.

Magnesium nitrate solution—Dissolve 20 g of magnesium nitrate ($Mg(NO_3)_2 \cdot 6H_2O$) with carbon dioxide-free water, and dilute with the same solvent to 100 mL. Immediately before use, dilute with carbon dioxide-free water 10 mL to 100 mL. A volume of 5 µL will provide 0.06 mg of $Mg(NO_3)_2$.

Apparatus—Use a suitable graphite furnace atomic absorption spectrometer equipped with a background compensation system, an autosampler, pyrolytically coated tubes or with pyrolytic graphite platforms, and a hollow-cathode lamp or electrodeless discharge lamp. Argon is used as the purge gas, and air is used as the alternate gas during the charring step. The flow rate is typically between 200 mL per minute and 300 mL per minute, but may be adapted according to the apparatus. Employ a wavelength of 283.3 nm.

Procedure—Separately inject 20 µL of the *Zero-setting solution,* the *Blank solution,* the *Test solution,* the *Reference solutions,* and add immediately 5 µL of *Magnesium nitrate solution,* which is used as matrix modifier, to each of the solutions. Inject each solution in triplicate. The ashing and atomization temperatures and times vary according to the apparatus, the background compensation system, the graphite tube, etc. The following parameters are given for guidance and need to be adjusted.

Heat the furnace progressively to 200° and maintain the drying temperature at 200° for 30 seconds, the ashing temperature at 750° for 40 seconds after a 40-second tempera-

ture rise, and the atomization temperature at 1800° for 10 seconds (0 seconds temperature rise). Clean out at 2600° for 7 seconds after a 1-second temperature rise.

Use the *Zero-setting solution* to set the instrument to zero. Calculate the mean readings of the *Test solution* and of the *Reference solutions* subtracting the mean blank. If necessary, dilute with the *Zero-setting solution* to obtain a reading within the linear range: the relative standard deviation of the three readings obtained for the triplicate injections of the *Test solution* and the *Reference solutions* to which the mean blank has been subtracted is not more than 15%; not more than 0.5 ppm of lead is found.

Reducing sugars—

Test solution—Dissolve 50.0 g of Sucrose in water, and dilute with the same solvent to 100.0 mL.

Procedure—Combine 5 mL of the *Test solution,* 5 mL of water, 1.0 mL of 1 M sodium hydroxide, and 1.0 mL of a 1 g per L solution of methylene blue in a test tube approximately 150 mm long and 16 mm in diameter. Mix, and place in a water bath. After exactly 2 minutes, take the tube out of the bath, and immediately examine the solution: the blue color does not disappear completely; ignore any blue color at the air/solution interface.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

GENERAL CHAPTERS

General Tests and Assays

Chemical Tests and Assays

LIMIT TESTS

BRIEFING

⟨**267**⟩ **Porosimetry by Mercury Intrusion,** page 893 of *PF* 28(3) [May–June 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this general test chapter. The presented text represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **Stage 3** draft. The proposed draft differs from the **Stage 3** draft by the reconsideration of the draft as a whole to take into consideration ISO Standards. A safety statement is added. Also, several editorial changes are made.

(ETM: J. Lane) RTS—42336-1

Add the following:

⟨267⟩ POROSIMETRY BY MERCURY INTRUSION

In general, different types of pores may be pictured as apertures, channels, or cavities within a solid body or as space (i.e., interstices or voids) between solid particles in a bed, compact, or aggregate. Porosity is a term that is often used to indicate the porous nature of solid material and is more precisely defined as the ratio of the volume of accessible pores and voids to the total volume occupied by a given amount of the solid. In addition to the accessible pores, a solid may contain closed pores, which are isolated from the external surface and into which fluids are not able to

penetrate. The characterization of closed pores, i.e., cavities with no access to an external surface, is not covered in this general chapter.

Porous materials may take the form of fine or coarse powders, compacts, extrudates, sheets, or monoliths. Their characterization usually involves the determination of the total pore volume or porosity as well as the pore size distribution.

It is well established that the performance of a porous solid (e.g., its strength, reactivity, permeability, or adsorbent power) is dependent on its pore structure. Many different methods have been developed for the characterization of pore structure. In view of the complexity of most porous solids, it is not surprising to find that the results obtained are not always in agreement and that no single technique can be relied upon to provide a complete picture of the pore structure. The choice of the most appropriate method depends on the application of the porous solid, its chemical and physical nature, and the range of pore size.

This chapter provides guidance for measurement of porosity and pore size distribution by mercury porosimetry. It is a comparative test, usually destructive in which the volume of mercury penetrating a pore or void is determined as a function of an applied hydrostatic pressure, which can be related to a pore diameter. Other information such as pore shape and interconnectivity, the internal and external surface area, powder granulometry, and bulk and tapped density can also be inferred from volume–pressure curves; however, these aspects of the technique do not fall under the scope of this chapter.

Practical considerations presently limit the maximum applied absolute pressure reached by some equipment to about 400 MPa, corresponding to a minimum equivalent pore diameter of approximately 0.003 µm. The maximum diameter will be limited for samples having a significant depth because of the difference in the hydrostatic head of mercury from the top to the bottom of the sample. For most purposes this limit may be regarded as 400 µm.

Inter-particle and intra-particle porosity can be determined, but the method does not distinguish between these porosities where they co-exist.

The method is suitable for the study of most porous materials. Samples that amalgamate with mercury, such as certain metals, may be unsuitable for this technique or may require a preliminary passivation. Other materials may deform or compact under the applied pressure. In some cases, it may be possible to apply sample compressibility corrections, and useful comparative data may still be obtained.

The mercury porosimetry technique should be considered to be comparative, because for most porous media, a theory is not available to allow an absolute calculation of results of pore size distribution. Therefore this technique is mainly recommended for development studies.

Mercury is toxic. Appropriate precautions must be observed to safeguard the health of the operator and others working in the area. Waste material must also be disposed of in a suitable manner, according to local regulations.

PRINCIPLE

The technique is based on the measurement of the mercury volume intruded into a porous solid as a function of the applied pressure. The measurement includes only those pores into which mercury can penetrate at the pressure applied.

A nonwetting liquid penetrates into a porous system only under pressure. The pressure applied is in inverse proportion to the inner width of the pore aperture. In the case of cylindrical pores, the correlation between pore diameter and pressure is given by the Washburn equation:

$$d_p = -\frac{4 \cdot \sigma}{p} \cos\theta \qquad (1)$$

p = applied pressure, in pascals,

d_p = pore diameter, in meters,

σ = surface tension of mercury, in newtons per meter,

θ = contact angle of mercury on the sample, in degrees.

APPARATUS

The sample holder, referred to as penetrometer or dilatometer, has a calibrated capillary tube, through which the sample can be evacuated and through which mercury can enter. The capillary tube is attached to a wider tube in which the test sample is placed. The change in the volume of mercury intruded is usually measured by the change in capacitance between the mercury column in the capillary tube and a metal sleeve around the outside of the capillary tube. If precise measurements are required, the internal volume of the capillary tube should be between 20% and 90% of the expected pore and void volume of the sample. Because different materials exhibit a wide range of open porosities, a number of penetrometers with different diameter capillary tubes and sample volumes may be required. A typical set-up for a mercury porosimeter instrument is given in *Figure 1*. The porosimeter may have separate ports for high- and low-pressure operation, or the low-pressure measurement may be carried out on a separate unit.

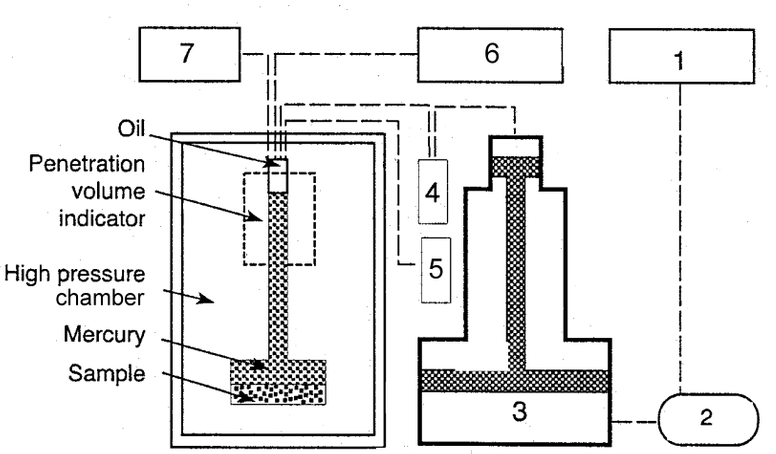


Fig. 1. Example of the set-up of a mercury porosimeter instrument.

METHOD

Sample Preparation—The sample is pretreated to remove adsorbed material that can obscure its accessible porosity by either heating and/or evacuation or by flowing inert gas. It may be possible to passivate the surface of wettable or amalgam-forming solids by producing a thin layer of oxide, or by coating with stearate. The sample of the pretreated solid is weighed and transferred to the penetrometer. The pore system of the sample is then degassed in a vacuum to a maximum residual pressure of 7 Pa.

Filling the Penetrometer with Mercury—Use mercury of analytical quality. The sample is overlaid with mercury under vacuum. The vacuum is required to ensure the transfer of mercury from the reservoir to the penetrometer. In a filled penetrometer, the filling pressure is comprised of the applied pressure plus the pressure contribution created by the head of mercury contacting the sample. A typical filling pressure would be about 5 kPa. The hydrostatic pressure of the mercury over the sample can be minimized by filling the penetrometer in the horizontal positions.

Low-Pressure Measurement—Admit air or nitrogen in a controlled manner to increase the pressure either in stages corresponding to the particular pore sizes of interest, or continuously at a slow rate. The concomitant change in the length of the mercury column in the capillary tube is recorded. When the maximum required pressure has been reached, reduce the pressure to ambient.

High-Pressure Measurement—After measurement at low-pressure conditions, the penetrometer filled with mercury is transferred to the high-pressure port or unit of the instrument and overlaid with hydraulic fluid. Mercury is intruded into the pore system via the hydraulic fluid. Increase the pressure in the system to the maximum pressure reached in the low-pressure measurement and record the intrusion volume at this pressure, because subsequent intrusion volumes are calculated from this initial volume. Increase the pressure either in stages corresponding to the particular pore sizes of interest, or continuously at a slow rate. The fall in the mercury column is measured up to the maximum required pressure. If required, the pressure may be decreased either in stages or continuously at a slow rate to determine the mercury extrusion curve. Make corrections to take account of changes in the volume of the mercury, the penetrometer, and other components of the volume detector system under elevated pressure. The extent of the corrections may be determined by means of blank measurements under the same conditions. An experimentally determined volume–pressure curve is shown in *Figure 2*.

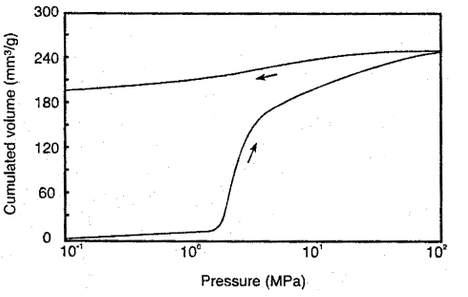


Fig. 2. Volume–pressure curve as semilogarithmic plot.

REPORTING OF RESULTS

The pressure readings are converted to pore diameter by means of the Washburn equation.

The surface tension of mercury σ depends not only on the temperature and the material, but also—in the case of markedly curved surfaces areas—on the radius of curvature. In general, values between $0.41\ N \cdot m^{-1}$ and $0.52\ N \cdot m^{-1}$ are measured at room temperature. If the value is not known, $\sigma = 0.48\ N \cdot m^{-1}$ can be used.

The contact angle of mercury θ in most cases is more than 90°. It may be determined using a contact angle instrument. If the θ value is not known, 140° can be used. Report the values of contact angle and surface tension used in the calculation. Visualization of the data can be done with several types of graphs. Frequently, in a graphical representation, the pore diameter is plotted on the abscissa and the dependent intruded specific volume on the ordinate to give the pore size distribution. It is appropriate here to choose a logarithmic scale for the abscissa (see *Figure 3*). The spaces between the particles of the solid sample are included as pores in the calculation. If the pores differ in size from the voids, the latter can be separated by choosing the relevant pore size range.

Extrusion curves may not be used for calculating the pore size distribution (for hysteresis, see *Figure 2*), because an intruded part of the mercury always remains in the pore system. The retention ratio may be useful for the qualitative characterization of pores that are only accessible via narrow openings (''ink-bottle pores'').

The most common characteristic values, such as the total intruded specific volume, the mean, and the median pore diameter are calculated from the pore size distribution. Moreover, sufficient information should be documented about the sample, the sample preparation, the evacuation conditions and the instrument used.

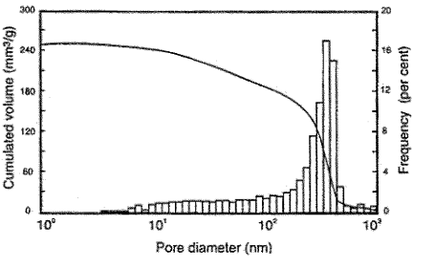


Fig. 3. Pore volume distribution as semilogarithmic plot.

CONTROL OF THE INSTRUMENT'S PERFORMANCE

As the mercury porosimetry technique is considered as a comparative test, no details are given in this chapter. However, it is recommended that a stable comparison material should be tested on a regular basis to monitor instrument calibration and performance.

Physical Tests and Determinations

BRIEFING

⟨**616**⟩ **Bulk Density and Tapped Density,** *USP 28* page 2379 and page 901 of *PF* 28(3) [May–June 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this general test chapter. The presented text represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **Stage 3** draft. The proposed draft differs from the USP chapter by the omission of *Methods 2* and *3* for both Bulk and Tapped Density. The Scott Volumeter was specific to USP and the vessel apparatus was specific to JP. Through harmonization efforts, the cylinder method is retained, because it is available in all regions. Also, several editorial changes are made.

(ETM: J. Lane) RTS—42336-2

Add the following:

⟨616⟩ BULK DENSITY AND TAPPED DENSITY

The bulk density of a powder is the ratio of the mass of a powder sample and its volume, including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per milliliter (g/mL) although the international unit is kilograms per cubic meter (1 g/mL = 1000 kg/m^3) because the measurements are made using cylinders.

The bulking properties of a powder are dependent upon the preparation, treatment, and storage of the sample, i.e., how it was handled. The particles can be packed to have a range of bulk densities and, moreover, the slightest disturbance of the powder bed may result in a changed bulk density. Thus, the bulk density of a powder is often very difficult to measure with good reproducibility and, in reporting the results, it is essential to specify how the determination was made.

The tapped density is an increased bulk density attained after mechanically tapping a graduated cylinder containing the powder sample. Because the interparticulate interactions influencing the bulking properties of a powder are also the interactions that interfere with powder flow, a comparison of the bulk and tapped densities can give a measure of the relative importance of these interactions in a given powder. Such a comparison is often used as an index of the ability of the powder to flow, which may be called "volume reduction index", as defined below.

BULK DENSITY

The bulk density of a powder is determined by measuring the volume of a known mass of powder sample, that may have been passed through a screen, into a graduated cylinder.

Procedure

Pass a quantity of powder sufficient to complete the test through a sieve with an aperture greater than or equal to 1.4 mm, if necessary, to break up agglomerates that may have formed during storage; this must be done gently to avoid changing the nature of the material. Into a dry graduated cylinder of 250 mL (readable to 2 mL), gently introduce, without compacting, approximately 100 g of the test sample (m) weighed with 0.1% accuracy. Carefully level the powder without compacting, if necessary, and read the unsettled apparent volume (V_0) to the nearest graduated unit. Calculate the bulk density, in g per mL, by the formula m/V_0. Generally, replicate determinations are desirable for the determination of this property.

If the powder density is too low or too high, such that the test sample has an untapped apparent volume of either more than 250 mL or less than 150 mL, it is not possible to use 100 g of powder sample. Therefore, a different amount of powder has to be selected as the test sample, such that its untapped apparent volume is 150 mL to 250 mL (apparent volume greater than or equal to 60% of the total volume of the cylinder); the mass of the test sample is specified in the expression of results.

TAPPED DENSITY

The tapped density is obtained by mechanically tapping a graduated measuring cylinder containing the powder sample. After observing the initial powder volume, the measuring cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop, under its own mass, a specified distance. Devices that rotate the cylinder during tapping may be preferred to minimize any possible separation of the mass during tapping down.

Apparatus

The apparatus (*Figure 1)* consists of the following:

— A 250-mL graduated cylinder (readable to 2 mL) with a mass of 220 ± 44 g; and

— A settling apparatus capable of producing, in 1 minute, either nominally 250 ± 15 taps from a height of 3 ± 0.2 mm, or nominally 300 ± 15 taps from a height of 14 ± 2 mm. The support for the graduated cylinder, with its holder, has a mass of 450 ± 10 g.

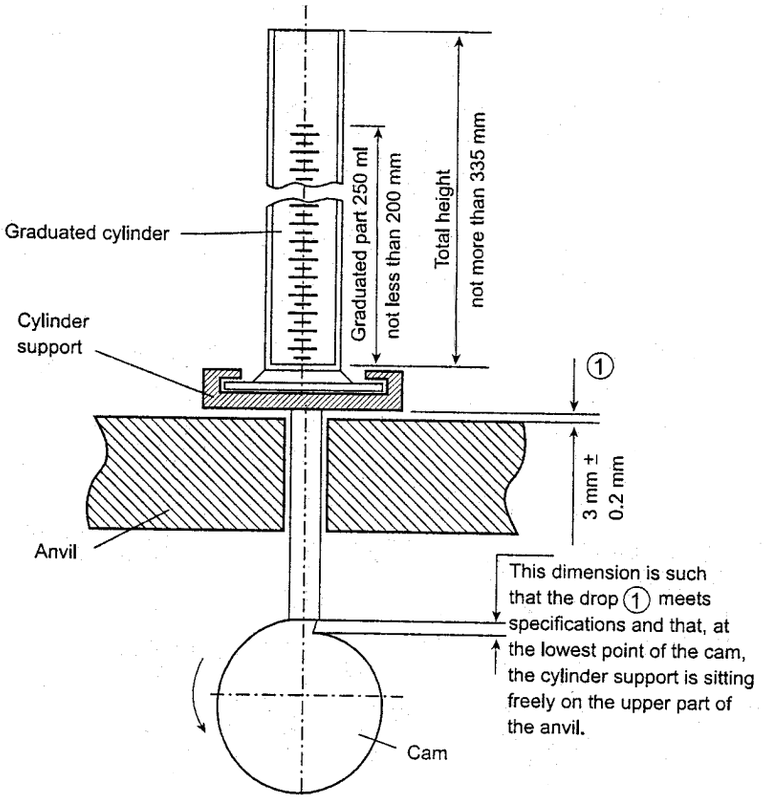


Fig. 1.

Procedure

Proceed as described above for the determination of the bulk volume (V_0). Secure the cylinder in the holder. Carry out 10, 500, and 1250 taps on the same powder sample and read the corresponding volumes V_{10}, V_{500}, and V_{1250} to the nearest graduated unit. If the difference between V_{500} and V_{1250} is less than 2 mL, V_{1250} is the tapped volume. If the difference between V_{500} and V_{1250} exceeds 2 mL, repeat in increments such as 1250 taps, until the difference between succeeding measurements is less than 2 mL. Note that fewer taps may be appropriate for some powders, when validated. Calculate the tapped density (g/mL) using the formula m/V_f, in which V_f is the final tapped volume. Generally, replicate determinations are desirable for the determination of this property.

MEASURES OF VOLUME REDUCTION INDEX

The volume reduction index and the Hausner Ratio are measures of the propensity of a powder to reduce its volume under mechanical tapping as described above. As such, they are measures of the powder ability to settle and they permit an assessment of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the volume reduction index and the Hausner Ratio.

Volume Reduction Index—Calculate by the formula:

$$\frac{100(V_0 - V_f)}{V_0}.$$

Hausner Ratio—Calculate by the formula:

$$\frac{V_0}{V_f}.$$

BRIEFING

⟨**699**⟩ **Density of Solids,** *USP 28* page 2410 and page 603 of *PF* 28(2) [Mar.–Apr. 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this general test chapter. The presented text represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **Stage 3** draft. The proposed draft differs from the USP chapter by the omission of the introductory section, which is informational. Also, several editorial changes are made.

(ETM: J. Lane) RTS—42307-1

Harmonization

Add the following:

⟨699⟩ DENSITY OF SOLIDS

GAS PYCNOMETRY FOR THE MEASUREMENT OF DENSITY

The test for gas pycnometric density of solids is intended to determine the volume occupied by a known mass of powder by measuring the volume of gas displaced under defined conditions. Hence, its pycnometric density is calculated.

Apparatus

The apparatus (see *Figure 1*) consists of the following:

— A sealed test cell, with an empty cell volume (V_c), connected through a valve to a reference cell, with a reference volume (V_r);

— A system capable of pressurizing the test cell with the measurement gas until a defined pressure (P), indicated by a manometer; and

— The system is connected to a source of measurement gas, which is preferably helium, unless another gas is specified.[1]

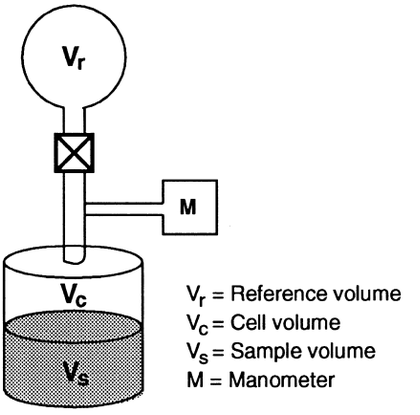


Fig. 1. Schematic of Gas Pycnometer.

The temperature of the gas pycnometer is between 15° and 30° and must not vary by more than 2° during the course of measurement.

The apparatus is calibrated, which means that the volumes (V_c) and (V_r) are determined, using a suitable reference standard, whose volume is known to the nearest 0.001 cm^3. The procedure described below is followed in two runs. First, with an empty test cell and second, with the reference standard placed in the test cell. The volumes (V_c) and (V_r) are calculated using the equation for the sample volume taking into account that the volume is zero in the first run.

Method

Weigh the test cell of the pycnometer and record the mass. Fill the test cell with a given mass of powder of the substance to be examined. Seal the test cell in the pycnometer. Record the system reference pressure (P_r) as indicated by the manometer while the valve that connects the reference cell with the test cell is open. Close the valve to separate the reference cell from the test cell. Pressurize the test cell with the gas to an initial pressure (P_i) and record the value obtained. Open the valve to connect the reference cell with

[1] If gases other than helium are used, it would not be surprising to obtain values different from those obtained with helium, since the penetration of the gas is dependent on the size of the pore as well as the cross-sectional area of the penetrating molecule. For example, the pycnometric volume will be overestimated by using nitrogen by comparison with helium, resulting in an underestimation of density.

the test cell. Record the final pressure (P_f). Repeat the measurement sequence for the same powder sample until consecutive measurements of the sample volume (V_s) agree to within 0.5%. The sample volume is expressed in cubic centimeters. Unload the test cell and measure the final powder mass (m) expressed in grams. If the pycnometer differs in operation or construction from the one shown in *Figure 1,* follow the instructions of the manufacturer of the pycnometer.

Expression of the Results

The sample volume (V_s) is given by the expression:

$$V_s = V_c - \frac{V_r}{\frac{P_i - P_r}{P_f - P_r} - 1}$$

The density (ρ) is given by the equation:

$$\rho = \frac{m}{V_s}$$

The sample conditioning is indicated with the results. For example, indicate whether the sample was tested as is or dried under specific conditions such as those described for *Loss on drying.*

It should be noted that the measured density is a volume weighted average of the densities of individual powder particles. The density will therefore be incorrect if the test gas sorbs onto the powder or if volatile contaminants are evolved from the powder during the measurement. Sorption is prevented by an appropriate choice of test gas. Helium is the common choice. Volatile contaminates in the powder are removed by degassing the powder under a constant purge of helium prior to the measurement. Occasionally, powders may have to be degassed under vacuum. Two consecutive readings must yield sample volumes that are equal within 0.2% if volatile contaminants are not interfering with the measurements. Because volatiles may be evolved during the measurement, weighing of the sample is done after the pycnometric measurement of volume.

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 (USP)

BRIEFING

Acetazolamide Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for acetazolamide is about 3.0 minutes.

(CRX: C. Okeke) RTS—42327-1

Add the following:

Acetazolamide Oral Suspension

» Acetazolamide Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetazolamide ($C_4H_6N_4O_3S_2$). Prepare Acetazolamide Oral Suspension 25 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Acetazolamide	2.5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF,* (1 : 1), or Cherry Syrup, *NF* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets place the Tablets in a mortar and comminute the Tablets to a fine powder, or add Acetazolamide powder. Add about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough liquid Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Acetazolamide RS.*

pH ⟨791⟩**:** between 4.0 and 5.0 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.1 and 3.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 4.1 g of anhydrous sodium acetate in 950 mL of water, add 20 mL of methanol, and 30 mL of acetonitrile, and mix. Adjust with glacial acetic acid to a pH of 4.0. Filter and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Transfer about 25 mg of USP Acetazolamide RS, accurately weighed, to a 50-mL volumetric flask, add 5.0 mL of 0.5 N sodium hydroxide, and mix to dissolve. Dilute with water to volume, and mix.

Standard preparation—Transfer 25.0-mL of the *Standard stock preparation* to a 50-mL volumetric flask, and dilute with water to obtain a solution having a known concentration of 250 µg per mL.

Assay preparation—Containers of Oral Suspension are agitated for 30 minutes on a rotating mixer before a 5-mL sample is removed. These samples are stored in clear glass vials at –70° until analyzed. At time of analysis remove the sample from the freezer and allow it to reach room temperature, mix with a vortex mixer for 30 seconds, and pipet 1.0 mL to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

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 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 retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 1.1%.

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 acetazolamide ($C_4H_6N_4O_3S_2$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Acetazolamide RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Alprazolam Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for alprazolam is about 10.0 minutes.

(CRX: C. Okeke) RTS—42327-2

Add the following:

Alprazolam Oral Suspension

» Alprazolam Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$). Prepare Alprazolam Oral Suspension 1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Alprazolam	100 mg
(Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Tablets in a suitable mortar, and comminute or triturate to a fine powder, or add Alprazolam powder. Add about 20 mL of the Vehicle, and mix until a uniform paste is formed. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature or under refrigeration.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Alprazolam RS.*

pH ⟨791⟩**:** between 4.2 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.4 and 4.2 (Cherry Syrup).

Beyond-use date: 45 days after the day on which it was compounded.

Assay—

Buffer solution—0.04 M sodium acetate solution adjusted with glacial acetic acid to a pH of 2.4.

Mobile phase—Prepare a filtered and degassed solution of *Buffer solution,* methanol, and acetonitrile (47 : 45 : 8). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Alprazolam RS in *Mobile phase,* and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Containers of Alprazolam Oral Suspension are agitated for 30 minutes on a rotating mixer before a 5-mL sample is removed. These samples are stored in clear glass vials at –70° until analyzed. At the time of analysis, remove the sample from the freezer and allow it to reach room temperature, mix with a vortex mixer for 30 seconds, and pipet 1.0 mL into a 50-mL volumetric flask. Dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 0.6 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 10 minutes, and the relative standard deviation for replicate injections is not more than 1.4%.

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 alprazolam. ($C_{17}H_{13}ClN_4$) in each mL of Oral Suspension taken by the formula:

$$50(C/V)(r_U/r_S),$$

In which C is the concentration, in µg per mL, of USP Alprazolam RS in the *Standard preparation;* V is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Azathioprine Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for azathioprine is about 4 minutes.

(CRX: C. Okeke) RTS—42327-3

Add the following:

Azathioprine Oral Suspension

» Azathioprine Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of azathioprine ($C_9H_7N_7O_2S$). Prepare Azathioprine Oral Suspension 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Azathioprine	5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,*	
a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, comminute them to a fine powder in a suitable mortar, or add Azathioprine powder to the mortar. Add about 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Azathioprine RS.*

pH ⟨791⟩**:** between 3.9 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.1 and 4.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 1.1 g of sodium 1-heptanesulfonate in 700 mL of water, add 300 mL of methanol, and mix. Adjust with 1 N hydrochloric acid to a pH of 3.5. Filter, and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve about 25 mg of USP Azathioprine RS, accurately weighed, in a 50-mL volumetric flask. Add about 15 mL of methanol and 0.5 mL of ammonium hydroxide to the flask, swirl and sonicate for 2 minutes. Dilute with methanol to volume, and mix. Transfer 10 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix.

Assay preparation—Containers of Oral Suspension are agitated for 30 minutes on a rotating mixer before a 5-mL sample is removed. These samples are stored in clear glass vials at –70° until analyzed. At the time of analysis, remove the sample from the freezer, and allow it to reach room temperature. Mix with a vortex mixer for 30 seconds, and pipet 1.0 mL into a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

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 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 retention time is about 4 minutes, and the relative standard deviation for replicate injections is not more than 1.3%.

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 azathioprine ($C_9H_7N_7O_2S$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Azathioprine RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Baclofen Oral Solution. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for baclofen is about 5.5 minutes.

(CRX: C. Okeke) RTS—42327-4

Add the following:

Baclofen Oral Solution

» Baclofen Oral Solution contains not less than 90 percent and not more than 110 percent of the labeled amount of baclofen ($C_{10}H_{12}ClNO_2$). Prepare Baclofen Oral Solution 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Baclofen	500 mg
Glycerin	5 mL
Syrup, *NF,* a sufficient quantity to make	100 mL

If using Tablets, comminute the Baclofen Tablets to a fine powder in a suitable mortar, or add Baclofen powder to the mortar. Add about 5 mL of the Glycerin to wet the powder, and triturate the powder to form a fine paste. Add about 5 mL of the Syrup to the paste, triturate well, and transfer, stepwise and quantitatively, the contents to a calibrated bottle. Rinse the mortar with additional portions of the Syrup, and transfer the contents to the container; repeat as necessary with sufficient Syrup to final volume.

Packaging and storage—Preserve in tight, light resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Baclofen RS.*

pH ⟨791⟩**:** between 5.0 and 6.0.

Beyond-use date: 35 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of 0.05 M monobasic sodium phosphate and acetonitrile (80 : 20) and adjust with phosphoric acid to a pH of 3.5. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Baclofen RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with water to obtain a solution having a known concentration of 5 µg per mL.

Assay preparation—Shake thoroughly by hand each bottle of Oral Solution. Pipet 0.5 mL of Oral Solution from each bottle to a 500-mL volumetric flask, dilute with water to volume to obtain a concentration of 5 µg per mL, and pass through a 0.22-µm polyvinylidenefluoride (PVDF) filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical 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 retention time is about 5.5 for baclofen; 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 responses for the major peaks. Calculate the quantity, in mg, of baclofen ($C_{10}H_{12}ClNO_2$) in the volume of Oral Solution taken by the formula:

$$1000(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Baclofen RS in the *Standard preparation; V* is the volume, in mL, of solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Bethanechol Chloride Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L##. The typical retention time for bethanechol chloride is about 3 minutes.

(CRX: C. Okeke) RTS—42327-5

Add the following:

Bethanechol Chloride Oral Suspension

» Bethanechol Chloride Oral Suspension contains not less than 90 percent and not more than 110 percent of the labeled amount of bethanechol chloride ($C_7H_{17}ClN_2O_2$). Prepare Bethanechol Chloride 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Bethanechol Chloride.	500 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Bethanechol Chloride Tablets, add to a suitable mortar and comminute to a fine powder, or add the Bethanechol Chloride powder to the mortar. Add about 20 mL of the Vehicle and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to final volume.

Packaging and storage—Preserve in tight, light resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Bethanechol Chloride RS.*

pH ⟨791⟩**:** between 4.0 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 2.6 and 3.4 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Acetonitrile and water (33 : 67). Filter and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in *Mobile phase,* and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 500 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 10-mL sample, and store in a clear glass vial at –70° until analyzed.

At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 5.0 mL of the sample into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L##. The flow rate is about 0.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 3.1%.

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 bethanechol chloride ($C_7H_{17}ClN_2O_2$) in the volume of Oral Suspension taken by the formula:

$$10(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Bethanechol Chloride RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Captopril Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for captopril is about 5.0 minutes.

(CRX: C. Okeke) RTS—42327-6

Add the following:

Captopril Oral Suspension

» Captopril Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of captopril ($C_9H_{15}NO_3S$). Prepare Captopril Oral Suspension 0.75 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Captopril	100 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension (1 : 1), *NF*, a sufficient quantity to make	134 mL

If using Tablets place the required number of Captopril Tablets in a suitable mortar and comminute to a fine powder, or add Captopril powder to the mortar. Add about 10 mL of the Vehicle and mix to a uniform paste. Add the remainder of the Vehicle in geometric portions, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a graduate. Add sufficient quantity of vehicle to final volume and transfer 100 mL to a calibrated bottle.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Captopril RS.*

pH ⟨791⟩**:** between 4.0 and 4.2 (Vehicle for Oral Solution and Vehicle for Oral Suspension).

Beyond-use date: 7 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (11 : 9) containing 0.5 mL of phosphoric acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Captopril RS in water to obtain a solution having a known concentration of 7.5 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical 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 retention time is about 5.0 minutes, 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, and measure the responses for the major peaks. Calculate the quantity, in mg, of captopril ($C_9H_{15}NO_3S$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Captopril RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ciprofloxacin Oral Solution. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for ciprofloxacin is about 5 minutes.

(CRX: C. Okeke) RTS—42327-7

Add the following:

Ciprofloxacin Oral Solution

» Ciprofloxacin Hydrochloride Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Ciprofloxacin Hydrochloride ($C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$).

Prepare Ciprofloxacin Hydrochloride Oral Solution 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Ciprofloxacin Hydrochloride	5 g
Vehicle for Oral Suspension, *NF*. . .	50 mL
Syrup, *NF,* a sufficient quantity to make	100 mL

If using Tablets, comminute the Tablets in a suitable mortar to a fine powder, or add Ciprofloxacin Hydrochloride powder to the mortar. Gradually add the Vehicle to the powder, and triturate well to a uniform paste. Add Syrup in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Syrup to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Ciprofloxacin RS.*

pH ⟨791⟩**:** between 4.0 and 5.0.

Beyond-use date: 50 days after the day on which it was compounded.

Assay—

Buffer solution—Prepare a solution of 5.5 mM monobasic potassium phosphate and 1.8 mM dibasic sodium phosphate adjusted to a pH of 7.4 by adding sodium hydroxide, and containing 5.5 mM hexadecyltrimethylammonium bromide.

Mobile phase—Prepare a solution of methanol and *Buffer solution* (65 : 35). Filter, and degas the *Mobile phase.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with water to obtain a solution having a known concentration of 5.0 µg per mL. The concentration of the working standard preparation is 5.0 µg per mL.

Assay preparation—Transfer by pipet about 1 mL of Oral Solution from each bottle to a suitable container, and dilute with water to obtain a concentration of 5 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector, a column heater maintained at 30°, and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the 5.0 µg per mL *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.5%.

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 responses for the major peaks. Calculate the quantity, in mg, of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in the volume of Oral Solution taken by the formula:

$$10000\,(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation;* V is the volume, in mL, of solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Clonazepam Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 10-cm column that contains 5-µm packing L1 (see *Chromatography* ⟨621⟩). The typical retention time for clonazepam is about 7 minutes.

(CRX: C. Okeke) RTS—1384-8

Add the following:

Clonazepam Oral Suspension

» Clonazepam Oral Suspension contains not less than 90 percent and not more than 110 percent of the labeled amount of clonazepam ($C_{15}H_{10}ClN_3O_3$). Prepare Clonazepam Oral Suspension 0.1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Clonazepam	10 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF,* (regular or sugar-free) and Vehicle for Oral Suspension, *NF,* or Cherry Syrup, *NF,* (1 : 1), a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, comminute the Tablets into a fine powder in a suitable mortar, or add Clonazepam powder to the mortar. Add approximately 10 mL of the vehicle, and mix to a uniform paste. Add the vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Clonazepam RS.*

pH ⟨791⟩**:** between 4.0 and 4.4 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 2.5 and 3.3 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of water, methanol, and acetonitrile (4 : 3 : 3). Filter and degas the *Mobile phase.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Clonazepam RS in acetonitrile to obtain a concentration of about 0.5 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with acetonitrile to obtain a solution having a known concentration of 25 µg per mL.

Assay preparation—Containers of Oral Suspension are agitated for 30 minutes on a rotating mixer before a 5-mL sample is removed. These samples are stored in clear glass vials at –70° until analyzed. At the time of analysis, remove the sample from the freezer and allow it to reach room temperature, mix with a vortex mixer for 30 seconds, and pipet 2.5 mL to a 10-mL volumetric flask. Dilute with acetonitrile to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm analytical 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 retention time of clonazepam is about 7 minutes; and the relative standard deviation for replicate injections is not more than 1.8%.

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 clonazepam ($C_{15}H_{10}ClN_3O_3$) in the volume of Oral Suspension taken by the formula:

$$4(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Clonazepam RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Diltiazem Hydrochloride Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for diltiazem is about 9.6 minutes.

(CRX: C. Okeke) RTS—42327-9

Add the following:

Diltiazem Hydrochloride Oral Suspension

» Diltiazem Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$). Prepare Diltiazem Hydrochloride Oral Suspension, 12 mg per mL, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Diltiazem Hydrochloride	1.2 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,*	
a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, comminute the Tablets to a fine powder in a suitable mortar or add Diltiazem Hydrochloride powder to the mortar. Add approximately 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle to the mortar in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Diltiazem Hydrochloride RS.*

pH ⟨791⟩**:** between 3.8 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.1 and 3.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Buffer solution—Dissolve 1.16 g of *d*-10-camphorsulfonic acid in 1000 mL of 0.1 M sodium acetate, adjust this solution by the addition of 0.1 N sodium hydroxide to a pH of 6.2, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, methanol, and *Buffer solution* (2 : 1 : 1). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Diltiazem Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 120 µg per mL.

Assay preparation—Containers of Oral Suspension are agitated for 30 minutes on a rotating mixer before a 5-mL sample is removed. These samples are stored in clear glass vials at –70° until analyzed. At time of analysis remove the sample from the freezer, allow it to reach room temperature, mix with a vortex mixer for 30 seconds, and pipet 1.0 mL to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the 100 µg per mL *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 9.6 minutes, and the relative standard deviation for replicate injections is not more than 1.3%.

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 diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Dipyridamole Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for dipyridamole is about 7.3 minutes.

(CRX: C. Okeke) RTS—42327-10

Add the following:

Dipyridamole Oral Suspension

» Dipyridamole Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dipyridamole ($C_{24}H_{40}N_8O_4$). Prepare Dipyridamole Oral Suspension 10 mg per mL as follows. See *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Dipyridamole	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,*	
a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Dipyridamole Tablets in a suitable mortar, and comminute to a fine powder, or add Dipyridamole powder to the mortar. Add about 20 mL of Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions, and mix well after each addition. Transfer, stepwise and quantitatively, to a graduated or a calibrated bottle. Add the Vehicle in portions to rinse the mortar, and add sufficient Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Dipyridamole RS.*

pH ⟨791⟩**:** between 3.9 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 250 mg of dibasic sodium phosphate in 250 mL of water, and adjust with dilute phosphoric acid (1 in 3) to a pH of 4.6. Add 750 mL of methanol, mix, and pass through a 0.5-µm membrane filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Dipyridamole RS in *Mobile phase* to obtain a suspension having a known concentration of 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 288-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7.3 minutes, and the relative standard deviation for replicate injections is not more than 2.3%.

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 dipyridamole ($C_{24}H_{40}N_8O_4$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Dipyridamole RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Dolasetron Mesylate Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 15-cm column that contains 5-µm packing L10. The typical retention time for dolasetron mesylate is about 6.9 minutes.

(CRX: C. Okeke) RTS—42327-11

Add the following:

Dolasetron Mesylate Oral Suspension

» Dolasetron Mesylate Oral Suspension contains not less than 90 percent and not more than 110 percent of the labeled amount of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S \cdot H_2O$). Prepare Dolasetron Mesylate Oral Suspension, 10 mg per mL, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Dolasestron Mesylate	1 g
Vehicle: a mixture of Vehicle for Oral Suspension, *NF* and Vehicle for Oral Solution, Sugar-Free, *NF* (1 : 1); or Strawberry Syrup and Vehicle for Oral Suspension, a sufficient quantity to make	100 mL

NOTE—If Strawberry Syrup, *NF* is used, it becomes a solution.

If using Tablets, comminute into a fine powder in a suitable mortar or add Dolasetron Mesylate powder. Mix separately Vehicle for Oral Suspen-

sion and Vehicle for Oral Solution, Sugar-Free, and stir vigorously; or mix with Strawberry Syrup. Add about 15 mL of the mixture to the powder and triturate well to a uniform paste. Transfer mortar contents, stepwise and quantitatively, to a calibrated bottle, rinse the mortar with about 15 mL of the Vehicle, and repeat the previous step as necessary to bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Dolasetron Mesylate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6.

Beyond-use date: 90 days after the day on which it was compounded.

Assay—

Buffer—Prepare a solution of 0.05 M ammonium acetate adjusted with diluted ammonium hydroxide to a pH of 7.5.

Mobile phase—Prepare a filtered and degassed solution of *Buffer* and acetonitrile (76 : 24). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Sample diluent—Prepare a solution of water and acetonitrile (76 : 24).

Standard stock preparation—Dissolve USP Dolasetron Mesylate RS in *Sample diluent* to obtain a solution having a known concentration of about 500 µg per mL.

Standard preparation—Transfer 2 mL of *Standard stock preparation* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 10 mL of this prepared solution to another 100-mL volumetric flask, and dilute with *Mobile phase* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer 1.0 mL of Oral Suspension by pipet to a 100-mL volumetric flask, and dilute with *Sample diluent* to obtain a 10 µg per mL concentration. Shake each sample thoroughly by hand for about 15 seconds, centrifuge at 1000 rpm for about 2 minutes, and assay the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm analytical column that contains 5-µm packing L10, and is maintained at a temperature of 30°. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 6.9 minutes, and the relative standard deviation for replicate injections is not more than 1.4%.

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 responses for the major peaks. Calculate the quantity, in mg, of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S \cdot H_2O$) in the volume of Oral Suspension taken by the formula:

$$1000(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Dolasetron 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.

BRIEFING

Flucytosine Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6- × 200-mm column that contains 5-µm packing L3. The typical retention time for flucytosine is about 3 minutes.

(CRX: C. Okeke) RTS—42327-12

Add the following:

Flucytosine Oral Suspension

» Flucytosine Oral Suspension contains not less than 90 percent and not more than 110 percent of the labeled amount of flucytosine ($C_4H_4FN_3O$). Prepare Flucytosine Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Flucytosine	2.5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Flucytosine Capsules, empty the appropriate amount into a suitable mortar, or add Flucytosine powder to the mortar. Add about 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Vehicle to bring to final volume.

Packaging and storage—Preserve in tight, light resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Flucytosine RS.*

pH ⟨791⟩**:** between 4.0 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.2 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Buffer—Dissolve 1g of ammonium acetate and 1 mL of diisopropylamine in one L of water, and adjust with glacial acetic acid to a pH of 7.5.

Mobile phase—Prepare a filtered and degassed solution of methanol and *Buffer* (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flucytosine RS in *Mobile phase,* and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer,

allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 0.5 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6- × 200-mm analytical column that contains 5-µm packing L3. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, 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 responses for the major peaks. Calculate the quantity, in mg, of flucytosine ($C_4H_4FN_3O$) in the volume of Oral Suspension taken by the formula:

$$200(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Flucytosine RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ganciclovir Oral Solution. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 10-cm column that contains 5-µm packing L1. The typical retention time for ganciclovir is about 3 minutes.

(CRX: C. Okeke) RTS—42327-13

Add the following:

Ganciclovir Oral Solution

» Ganciclovir Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ganciclovir ($C_9H_{13}N_5O_4$). Prepare Ganciclovir Oral Solution, 100 mg per mL, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Ganciclovir	10 g
Vehicle for Oral Solution, *NF* (regular or sugar-free), a sufficient quantity to make . . .	100 mL

If using Capsules, empty the contents of the Capsules into a suitable mortar, or add Ganciclovir powder to the mortar. Add sufficient Vehicle to wet the powder, and work to a smooth paste. Add additional Vehicle to about half the final volume, and transfer the contents of the mortar to a calibrated bottle. Using additional Vehicle, rinse out the mortar and transfer the contents, stepwise and quantitatively, to bring to final volume.

[Caution—Avoid skin contact or inhalation of ganciclovir by using protective gloves and a fume hood or surgical mask.]

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

Labeling—Label it to state that it is to be well shaken before use, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Ganciclovir RS.*

pH ⟨791⟩**:** between 4.0 and 5.0.

Beyond-use date: 90 days after the day on which it was compounded.

Assay—

25 mM Monobasic sodium phosphate buffer—Prepare this buffer and adjust with phosphoric acid to a pH of 2.5.

Mobile phase—Prepare a solution of *25 mM Monobasic sodium phosphate buffer* and acetonitrile (97.5 : 2.5). Filter, and degas the *Mobile phase.* Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Sample diluent—Prepare a solution of water, acetonitrile, and methanol (80 : 15 : 5).

Internal standard solution—Prepare a 4 mg per mL aqueous solution of hypoxanthine.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Ganciclovir RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Transfer an appropriate volume of *Standard stock preparation* to a suitable container, and add an appropriate volume of *Internal standard solution* to obtain a solution having known concentrations of 6 µg per mL and 4 µg per mL, respectively.

Assay preparation—Transfer about 1 mL of Oral Solution from each bottle to a plastic weighing cup, and weigh to determine density. [NOTE—The exact volume of Oral Solution taken from each bottle is calculated by the suspension density.] Transfer the suspension to a 100-mL volumetric flask, and add about 50 mL of water. Place the volumetric flask on a mechanical shaker for 30 minutes, and then dilute with water to volume. Transfer 0.6 mL from this solution and 1 mL of the *Internal standard solution* to a 100-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm analytical column that contains 5-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 relative retention time for ganciclovir is 1.0, and 0.75 for hypoxanthine; 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 ganciclovir ($C_9H_{13}N_5O_4$) in the volume of Oral Solution taken by the formula:

$$100(C/V)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Ganciclovir RS in the *Standard preparation; V* is the volume, in mL, of solution taken; and R_U and R_S are the peak response ratios of the analyte peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Isradipine Oral Solution. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for isradipine is about 6.0 minutes.

(CRX: C. Okeke) RTS—42327-14

Add the following:

Isradipine Oral Solution

» Isradipine Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isradipine ($C_{19}H_{21}N_3O_5$). Prepare Isradipine Oral Solution 1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Isradipine	100 mg
Glycerin	5 mL
Syrup, *NF*, a sufficient quantity to make	100 mL

If using Capsules, empty the contents of the Isradipine Capsules into a suitable mortar, or add Isradipine powder to the mortar. Add about 5 mL of Glycerin to wet the powder, and triturate to a fine paste. Add about 15 mL of Syrup to the paste, triturate well, and then transfer the contents to a calibrated bottle. Rinse the mortar with additional portions of Syrup, and transfer the contents, stepwise and quantitatively, and bring to final volume.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Isradipine RS.*

pH ⟨791⟩**:** between 5.0 and 7.0.

Beyond-use date: 35 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of methanol, water, and tetrahydrofuran (42 : 38 : 20). Filter and degas the *Mobile phase.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: methanol and alcohol (1 : 1).

Standard stock solution—Dissolve an accurately weighed quantity of USP Isradipine RS in *Diluent* to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with *Diluent* to obtain a solution having a known concentration of 100 µg per mL

Assay preparation—Pipet 1.0 mL of Oral Solution from each bottle to a 10-mL volumetric flask, and dilute with *Diluent* to volume to obtain a concentration of 100 µg per mL. Pass through a 0.22-µm polyvinylidenefluoride (PVDF) filter prior to injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm analytical 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 retention time is about 6.0 minutes for isradipine; 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 isradipine ($C_{19}H_{21}N_3O_5$) in the volume of Oral Solution taken by the formula:

$$10(C / V)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Isradipine RS in the *Standard preparation;* V is the volume, in mL, of solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Labetalol Hydrochloride Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1 (see *Chromatography* ⟨621⟩). The typical retention time for labetalol is about 7.5 minutes.

(CRX: C. Okeke) RTS—42327-15

Add the following:

Labetalol Hydrochloride Oral Suspension

» Labetalol Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$). Prepare Labetalol Hydrochloride Oral Suspension 40 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Labetalol Hydrochloride	4 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Labetalol Hydrochloride Tablets in a suitable mortar. Comminute the Tablets to a fine powder or add Labetalol Hydrochloride powder. Add about 20 mL of the Vehicle and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the Vehicle in portions to rinse the mortar, and combine with the final preparation to final volume and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Labetalol Hydrochloride RS.*

pH ⟨791⟩**:** between 4.0 and 5.0 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 0.1 M monobasic sodium phosphate and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Labetolol Hydrochloride RS in water to obtain a solution having a known concentration of 400 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7.5 minutes, and the relative standard deviation for replicate injections is not more than 1.6%.

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 labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Labetalol RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Levothyroxine Sodium Oral Solution. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L10. The typical retention time for levothyroxine sodium is about 7.6 minutes.

(CRX: C. Okeke) RTS—42327-16

Add the following:

Levothyroxine Sodium Oral Solution

» Levothyroxine Sodium Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$). Prepare Levothyroxine Sodium Oral Solution 25 µg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Levothyroxine Sodium	2.5 mg
Glycerin, *NF*	40 mL
Purified Water, a sufficient quantity to make	100 mL

If using Tablets place the Tablets in a suitable mortar. Using a pestle, break the Tablets and pulverize them to a fine powder, or add Levothyroxine Sodium powder. Add the Glycerin, triturate the powder into a pourable suspension, and transfer, stepwise and quantitatively, to a graduated container. Rinse the mortar with portions of Purified Water. Add Purified Water to the preparation to final volume, and mix well. Package and label.

Packaging and storage—Preserve in tight, light-resistant, high-density polyethylene containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken before use.

USP Reference standards ⟨11⟩**—***USP Levothyroxine RS. USP Liothyronine RS.*

pH ⟨791⟩**:** between 6.5 and 7.0.

Beyond-use date: 8 days after the day on which it was compounded.

Limit of liothyronine sodium—*Mobile phase, Standard liothyronine preparation,* and *Chromatographic system—* Proceed as directed in the *Assay.*

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

Procedure—Proceed as directed in the *Assay.* Calculate the quantity, in µg, of liothyronine sodium ($C_{15}H_{11}I_3NNaO_4$) in the Oral Solution taken by the formula:

$$(672.96/650.98)C(r_U/r_S),$$

in which 672.96 and 650.98 are the molecular weights of liothyronine sodium and liothyronine, respectively; C is the concentration, in µg per mL, of USP Liothyronine RS in the *Standard liothyronine preparation;* and r_U and r_S are the liothyronine peak responses obtained from the *Test preparation* and the *Standard liothyronine preparation,* respectively: not more than 2.0% of liothyronine is found.

Assay—

Mobile phase—Prepare a solution of water, acetonitrile, and phosphoric acid (65 : 35 : 1). Filter and degas the *Mobile phase.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Levothyroxine stock preparation—Dissolve an accurately weighed quantity of USP Levothyroxine RS in water to obtain a concentration of about 100 µg per mL.

Levothyroxine standard preparation—Dilute the *Levothyroxine stock preparation* with water to obtain a solution having a known concentration of 25 µg per mL

Liothyronine stock preparation—Dissolve an accurately weighed quantity of USP Liothyronine RS in water to obtain a solution having a known concentration of 100 µg per mL.

Liothyronine standard preparation—Dilute the *Liothyronine stock preparation* with water to obtain a solution having a known concentration of 25 µg per mL

Assay preparation—Remove a 1-mL sample of the Oral Solution from each bottle after inverting the bottle by hand 30 times, place the sample into 2-mL freezing vials, and freeze at –80° until analyzed. Thaw samples at room temperature, mix thoroughly with a vortex mixer, and centrifuge at 2500 rpm for 5 minutes. The supernatant is used for the sample injection into the chromatographic system.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L10. The flow rate is about 1.0 mL per minute. Chromatograph the *Levothyroxine standard preparation* and the *Liothyronine standard preparation,* and record the peak responses as directed for *Procedure:* the retention times for levothyroxine and liothyronine are about 7.6 and 6.2 minutes, respectively; and the relative standard deviation for replicate injections is not more than 5.2%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Levothyroxine 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 ($C_{15}H_{10}I_4NNaO_4$) in the volume of Oral Solution taken by the formula:

$$(798.85 / 776.87)\,(C / V)(r_U / r_S),$$

in which 798.85 and 776.87 are the molecular weights of levothyroxine sodium and levothyroxine, respectively; C is the concentration, in mg per mL, of USP Levothyroxine RS in the *Levothyroxine standard preparation; V* is the volume, in mL, of solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Levothyroxine standard preparation,* respectively.

BRIEFING

Metolazone Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 20-cm column that contains 5-µm packing L3. The typical retention time for metolazone is about 6.0 minutes.

(CRX: C. Okeke) RTS—42327-17

Add the following:

Metolazone Oral Suspension

» Metolazone Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Metolazone. ($C_6H_9N_3O_3$). Prepare Metolazone Oral Suspension 1mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Metolazone	100 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF*, a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Metolazone Tablets in a suitable mortar, and comminute to a fine powder, or add Metolazone powder to the mortar. Add about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions, and transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add suffi-

cient Vehicle in portions to rinse the mortar. Add to the preparation to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Metolazone RS.*

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 2.5 and 3.3 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 700 mL methanol, 300 mL of 1.5 g ammonium acetate, and 1 mL of diisopropylamine. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Metolazone RS in water to obtain a solution having a known concentration of 1.0 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 1000-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 20-cm analytical column that contains 5-µm packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for metolazone is about 6.0 minutes, and the relative standard deviation for replicate injections is not more than 2.2%.

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 metolazone ($C_6H_9N_3O_3$) in the volume of Oral Suspension taken by the formula:

$$1000(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Metolazone RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Metoprolol Tartrate Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for metoprolol tartrate is about 7.3 minutes.

(CRX: C. Okeke) RTS—42327-18

Add the following:

Metoprolol Tartrate Oral Suspension

» Metoprolol Tartrate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Metoprolol Tartrate. $((C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6)$. Prepare Metoprolol Tartrate Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Metoprolol Tartrate	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Metoprolol Tartrate Tablets in a suitable mortar, and comminute the tablets, or add Metoprolol Tartrate powder. Add the Vehicle in geometric portions, and mix well. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the Vehicle in portions to rinse the mortar. Add to the preparation to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or under refrigeration.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Metoprolol Tartrate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed solution by dissolving 961 mg of 1-pentanesulfonic acid sodium salt, monohydrate, and 82 mg of anhydrous sodium acetate in a mixture of 550 mL of methanol, 470 mL of water, and 0.57 mL of glacial acetic acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Metoprolol Tartrate RS in water to obtain a solution having a known concentration of 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

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 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 retention time

for metoprolol tartrate is about 7.3 minutes; and the relative standard deviation for replicate injections is not more than 1.3%.

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 metoprolol tartrate $((C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6)$ in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Metoprolol Tartrate RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Norfloxacin Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 150-mm column that contains 5-µm packing L11. The typical retention time for norfloxacin is about 3.5 minutes.

(CRX: C. Okeke) RTS—42327-19

Add the following:

Norfloxacin Oral Suspension

» Norfloxacin Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Norfloxacin. ($C_{16}H_{18}FN_3O_3$). Prepare Norfloxacin Oral Suspension 20 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Norfloxacin	2 g
Vehicle for Oral Suspension, *NF*. . .	50 ml
Strawberry Syrup: a mixture of	
3200 mL Syrup, *NF* and	
600 mL Strawberry Syrup, *NF,*	
a sufficient quantity to make	100 mL

If using Tablets, place the Norfloxacin Tablets in a suitable mortar and comminute well, or add Norfloxacin powder. Levigate with the Vehicle, using geometric proportions. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the Strawberry Syrup in portions to rinse the mortar, and add to the preparation to final volume, and mix well.

Packaging and storage—Preserve in tight light-resistant containers. Store at controlled room temperature.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Norfloxacin RS.*

pH ⟨791⟩**:** between 5.3 and 6.3.

Beyond-use date: 30 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of 94 mM monobasic potassium phosphate, acetonitrile, methanol, and trifluoroacetic acid (80 : 15 : 5 : 0.3). Filter, and degas the *Mobile phase.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Sample diluent: water, acetonitrile, and methanol (80 : 15 : 5).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Norfloxacin RS in 0.1 N hydrochloric acid to obtain a concentration of about 500 µg per mL.

Standard preparation—Dilute the *Standard stock preparation* with *Sample diluent* to obtain a solution having a known concentration of 5 µg per mL

Assay preparation—Pipet 250 µL of Oral Suspension from each bottle to a 10-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume. Agitate the sample on a vortex mixer to ensure dissolution of Norfloxacin. Pipet 100 µL of this solution into a 10-mL volumetric flask, and dilute with *Sample diluent* to volume to obtain a concentration of 5 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 150-mm analytical column that contains 5-µm packing L11. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3.3 for norfloxacin; 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 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 norfloxacin ($C_{16}H_{18}FN_3O_3$) in the volume of Oral Suspension taken by the formula:

$$4000(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Norfloxacin RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ondansetron Hydrochloride Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 3.9-mm × 20-mm guard column that contains 4-µm packing L10, and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L10. The typical retention time for Ondansetron Hydrochloride is about 30 minutes.

(CRX: C. Okeke) RTS—42327-20

Add the following:

Ondansetron Hydrochloride Oral Suspension

» Ondansetron Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of on-

dansetron hydrochloride. ($C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$). Prepare Ondansetron Hydrochloride Oral Suspension 0.8 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Ondansetron Hydrochloride	80 mg
Vehicle for Oral Suspension, *NF* Vehicle for Oral Solution, *NF* (regular or sugar-free) (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Tablets, place the Tablets in a suitable glass mortar, and comminute well, or add Ondansetron Hydrochloride powder. In 5 mL portions, add the mixed Vehicle for Oral Suspension, and mix well. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the mixed Vehicle for Oral Suspension in geometric portions to rinse the mortar, and add to the preparation to final volume, and mix well. If using Cherry Syrup, repeat as above, replacing mixed Vehicle for Oral Suspension with Cherry Syrup.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Ondansetron Hydrochloride RS.*

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.0 and 4.0 (Cherry Syrup).

Beyond-use date: 42 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of 43 mM monobasic potassium phosphate buffer adjusted with a mixture of 1 N sodium hydroxide and acetonitrile (85 : 15) to a pH of 5.4. Filter and degas the solution. 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* to obtain a solution having a known concentration of about 4 µg per mL.

Assay preparation—After each amber plastic vial containing Oral Suspension that is stored at 4° is brought to room temperature, pipet 500 µL of Oral Suspension from each bottle into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a 0.45-µm filter and keep frozen at –70° until assayed.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector, a 3.9-mm × 20-mm guard column that contains 4-µm packing L10, and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L10. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 30 minutes for ondansetron hydrochloride; and the relative standard deviation for replicate injections is not more than 1.6%.

Procedure—Separately inject equal volumes (about 80 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 ondansetron hydrochloride ($C_{18}H_{19}N_3O$) in the volume of Oral Suspension taken by the formula:

$$200(C/V)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Ondansetron Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Quinidine Sulfate Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 10-cm column that contains 5-µm packing L1. The typical retention time for quinidine sulfate is about 8.5 minutes.

(CRX: C. Okeke) RTS—42327-21.

Add the following:

Quinidine Sulfate Oral Suspension

» Quinidine Sulfate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of quinidine sulfate ($(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$). Prepare Quinidine Sulfate Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Quinidine Sulfate	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Quinidine Sulfate Tablets, place in a suitable mortar, and comminute into a fine powder, or add Quinidine Sulfate powder to the mortar. Add about 15 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in geometric portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to the calibrated bottle. Add sufficient Vehicle to volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Quinindine Sulfate RS.*

pH ⟨791⟩**:** between 3.4 and 4.4 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.2 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Methanesulfonic acid solution—Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, dilute with water to 500 mL, and mix.

Diethylamine solution—Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.

Mobile phase—Prepare a suitable filtered and degassed solution of water, acetonitrile, *Methanesulfonic acid solution*, and *Diethylamine solution* (80 : 20 : 2 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Quinidine Sulfate RS in *Mobile phase* to obtain a solution having a known concentration of about 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the 100 µg per mL *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for quinidine sulfate is about 8.5 minutes, 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 responses for the major peaks. Calculate the quantity, in mg, of quinidine sulfate $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$ in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Quinidine Sulfate RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Sumatriptan Succinate Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 10-cm column that contains 5-µm packing L1. The typical retention time for sumatriptan succinate is about 11 minutes.

(CRX: C. Okeke) RTS—42327-22

Add the following:

Sumatriptan Succinate Oral Suspension

» Sumatriptan Succinate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sumatriptan succinate ($C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$). Prepare Sumatriptan Succinate Oral Suspension 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Sumatriptan Succinate	500 mg
Vehicle for Oral Suspension, *NF* . . .	25 mL
Vehicle for Oral Solution, *NF* (regular or sugar-free), a sufficient quantity to make	100 mL

If using Tablets, comminute into a fine powder using a suitable mortar, or add Sumatriptan Succinate powder to the mortar. Add about 25 mL of the Vehicle for Oral Suspension in 5-mL portions, mixing thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle for Oral Solution to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at a controlled room temperature or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Sumatriptan Succinate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6.

Beyond-use date: 14 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of 0.01 M dibutylamine in 0.025 M aqueous monobasic sodium phosphate dihydrate and acetonitrile (75 : 25). Adjust with 1 N sodium hydroxide to a pH of 8.0, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve an accurately weighed quantity of *N*-hydroxymethylsumatriptan in *Mobile phase* to obtain a known concentration of about 3.0 mg per mL.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Sumatriptan Succinate RS in *Mobile phase* to obtain a known concentration of about 4.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with *Mobile phase* to obtain a solution having a known concentration of about 120 µg per mL. Each solution contains 30 µg per mL of *Internal standard solution.*

Assay preparation—Transfer about 1 mL of Oral Suspension from each bottle to a suitable container, and dilute with 0.1 M hydrochloric acid to obtain a concentration of about 0.15 mg per mL. Pass the solution through a 0.22-µm filter into a 0.3-mL polypropylene sample vial for assay.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 282-nm detector and a 4.6-mm × 10-cm analytical column that contains 5-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 retention times for sumatriptan and *N*-hydroxymethylsumatriptan are 11 and 14 minutes respectively; 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 sumatriptan succinate ($C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Sumatriptan Succinate RS in the *Standard preparation; V* is the volume, in mL, of suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Verapamil Hydrochloride Oral Suspension. Because there is no existing *USP* monograph for this dosage form, the following new monograph is being previewed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm column that contains 5-µm packing L1. The typical retention time for verapamil hydrochloride is about 4.8 minutes.

(CRX: C. Okeke) RTS—42327-25

Add the following:

Verapamil Hydrochloride Oral Suspension

» Verapamil Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$). Prepare Verapamil Hydrochloride Oral Suspension 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Verapamil Hydrochloride	5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free) and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—If Cherry Syrup, *NF* is used, it becomes a solution.

If using Verapamil Hydrochloride Tablets, comminute to a fine powder using a suitable mortar, or add Verapamil Hydrochloride powder. Add about 40 mL of the Vehicle in geometric portions, and mix to obtain a uniform paste. Transfer the mortar contents, stepwise and quantitatively, to a calibrated bottle. Add the Vehicle in portions to rinse the mortar, add sufficient Vehicle to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Verapamil Hydrochloride RS.*

pH ⟨791⟩**:** between 3.8 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of .01 M sodium acetate with a mixture of acetic acid having a concentration of 33 mL per L, acetonitrile, and 2-aminoheptane (50 : 50 : 0.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Verapamil Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 500 µg per mL.

Assay preparation—Agitate containers of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, store in a clear glass vial at –70° until analyzed. At time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL into a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for verapamil hydrochloride is about 4.8 minutes, and the relative standard deviation for replicate injections is not more than 0.7%.

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 verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Verapamil Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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

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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.

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Process Characterization and Validation for Protein Products

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ABSTRACT Process characterization and validation are essential to the production of quality proteins from both recombinant and natural sources. This *Stimuli* article describes approaches for studies to validate and optimize manufacturing processes at various stages of a protein product's life cycle. A proposed new *USP* General Chapter will provide general guidance on the extent of process characterization necessary at each stage of the protein product's life cycle. A life-cycle approach to process validation not only spares precious research resources but also allows the experimentation necessary to develop robust processes that produce quality protein products. Readers are invited to submit comments, suggested additions, changes, and revisions.

INTRODUCTION

Quality cannot be inspected or tested into a product, but instead it must be achieved by design and control of the manufacturing process, which consists of: (1) detailed instructions for carrying out the defined manufacturing process, (2) comprehensive in-process monitoring and quality controls, (3) final product testing, and (4) process validation.

Process validation is establishing documented evidence that provides a high degree of assurance that a specific process operated within established parameters performs effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes. Process validation is not simply a three-batch study but is instead a life-cycle concept that starts with preliminary process controls for products used in Phase 1 clinical studies, continual process characterization during clinical development, formal process validation studies for market approval, and continuing revalidation throughout the lifetime of the manufacturing process.

There are three approaches to process validation: (1) prospective (process validation conducted prior to product distribution), (2) concurrent (process validation conducted during routine production), and (3) retrospective, (process validation conducted for a product already in distribution). Prospective process validation is the preferred approach, but in some exceptional cases concurrent process validation can be justified (e.g., limited or infrequent manufacturing runs). Only rarely is retrospective process validation justifiable (e.g., for well-established processes). Regardless of the validation approach used, the following validation elements are required: preapproved written validation protocol with predefined acceptance criteria, followed by a reviewed and approved written validation report.

The complex nature of macromolecular pharmaceuticals of biological and biotechnological origin requires rigorous design and control of the manufacturing process. The purpose for this proposed *USP* General Chapter is to provide general guidelines for carrying out process validation on biological/biotech specific manufacturing processes.

PHASE 1

Phase 1 clinical studies are designed to assess product safety and occasionally to determine the maximum tolerated dose (MTD) for a given substance. Process development is an on-going activity, and no expectations should exist that the final process, specifications, or product assays will be set on material used in Phase 1 trials. In some instances, early Phase 1 work is performed at academic centers where the product is manufactured in a laboratory rather than a GMP facility. In these cases, the facility and/or processes used during Phase 1 are unlikely to be used in subsequent clinical studies.

At early stages of the product life cycle, a balance must be met between process development, setting of specifications, and initiating assay development and validation. These activities should be pursued early enough to accelerate development of products that turn out to be clinically and economically viable, while at the same time not so early that full-scale process and assay validation activities are conducted for unproven products. This balance will likely vary between individual products and corporate development strategies, but at a minimum they should include consistent production of the active pharmaceutical ingredient (API) with similar or improving quality attributes, setting reasonable and achievable interim specifications, and qualification of critical assays needed to define safety and potency. Critical assays should be sufficiently robust and reproducible to allow comparisons between early-phase product and

[*] The views presented in this article do not necessarily reflect those of FDA. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

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product made for later clinical trials if development proves successful. Careful documentation of the development program and archiving of data, process, and final product samples are also important in maintaining continuity if development progresses beyond Phase 1.

Regulatory requirements for product and process characterization in Phase 1 focus on product safety rather than in-depth characterization of the physico-chemical and biological attributes of the product. Detailed molecular characterization of the API, although important, generally is not needed for material used in Phase 1 studies (*1*). Examples of safety requirements prior to the initiation of the Phase 1 study include validation of the removal of murine retroviruses and other viruses by the purification process. This is required because rodent cell lines, such as Chinese hamster ovary (CHO) cells and murine hybridomas spontaneously produce endogenous type C retrovirus particles because their genomes contain dozens of copies of retroviral sequences. Harvests from mammalian cell cultures can be expected to contain some level of type C particles, and the purification process should be demonstrated to be able to remove sufficient particles to ensure that fewer than one dose in every one million will potentially contain one viral particle.

Other microbiological considerations in Phase 1 include testing harvests and cell banks for potential bacterial, fungal, or viral contaminants. The scope of testing required for marketed products is described in the International Conference on Harmonization (ICH) Q5A document (*2*). At a minimum in Phase 1 the cell banks should be screened for sterility, and freedom from mycoplasma and adventitious viruses using in vitro co-cultivation assays. Cell culture harvests should be screened routinely for mycoplasma and adventitious viruses using in vitro co-cultivation assays. To prevent introduction of Transmissible Spongiform Encephalopathies (TSEs) into the product, animal-derived raw materials should not be sourced from countries under USDA import ban. Products made with primate-derived cell lines should be stringently screened for relevant human pathogens (*1, 2*). Finally, bioburden in intermediates during downstream processing should be minimized in order to prevent significant introduction of endotoxin or other bacterial contaminants into intermediates or the final product. For drugs intended for parenteral use, it is expected that product in its final dosage form will be sterile filtered into sterile container/closure systems in class 100 conditions. During Phase 1, it is acceptable to perform this process manually in class 100 laminar-flow tissue culture hoods if no other facility is available (e.g., at an academic institution).

Other product safety considerations in Phase 1 are likely to be product specific. For example, oncology products such as anti-tumor monoclonal antibody–toxin complexes may have presumed effective doses close to the MTD. In these cases, having a highly precise and reproducible potency assay is particularly critical to avoid overdosing. Product mix-ups at multi-product or contract facilities producing several products such as multiple monoclonal antibodies could easily confound clinical studies and raise safety issues. A highly specific identity test in this case would be the front line against potential product mix-ups and would be expected by regulatory authorities.

Stability studies should be initiated immediately before Phase 1 studies. These stability studies should focus on continued product stability during the clinical trials. However, it is not too early to start to define stability-indicating assays, determine optimal storage conditions, and start developing formulations that maximize stability of the API.

PHASE 2

Many products fail in early clinical studies; therefore, due to economic reasons extensive process validation studies beyond safety considerations do not start until there is a reasonable certainty that the drug candidate will progress to market. Typically these activities are not initiated until late in Phase 2 trials or early in the pivotal trials. Starting process validation too early in the development process may lead to repeating many of the studies; waiting to start process validation may delay a regulatory submission and final drug approval. Preliminary characterization of the process should be initiated sometime during Phase 2 trials. The challenge during Phase 2 is to optimize the time and cost of process development. Data collected during the process characterization stage provide a basis for developing the commercial process and will serve as the foundation for later process validation studies.

Manufacturing of the product used in Phase 2 trials typically occurs at pilot scale and only rarely at laboratory or commercial scale. Equipment used in manufacturing the drug substance and drug product should be qualified to ensure that data collected from the process can satisfactorily be evaluated and transferred when the process is scaled up and validated. For example, culture conditions collected during fermentation—including pH, temperature, dissolved oxygen, and feed rates—can be evaluated only if adequate calibration of the monitoring equipment has been performed. Monitoring the quality of intermediates, final product, and equipment operating parameters during the manufacture of developmental and clinical trail batches facilitates later identification of critical parameters that influence the quality of the drug and affect the reproducibility of the process. Critical operating parameters usually are determined by analyzing data that affect the physico-chemical and biological characteristics, impurity profile, or yield of the product.

Development activities for the product used in early Phase 2 studies should emphasize developing and qualifying analytical methods and reference standard to adequately identify the quality of drug substance intermediates, drug substance, and the drug product. For example, if a process change increases the yield at a specific step, the level of product- and/or process-related impurities also may increase. Without adequate methods to evaluate the quality of intermediates and final product, changes to the process may lead to a product with levels of impurities and related substances that are outside qualified levels. As changes are made to the manufacturing process, levels of impurities

should not exceed drug product levels used in the pharmacology/toxicology and clinical studies. The driving force for collecting manufacturing data in early product development is to collect of body of knowledge about the process, develop an understanding of each unit operation, determine the level of clearance of impurities at each step, justify process adjustments during scale-up, identify critical control points and operating ranges that will be monitored later in the commercial process, and determine how and if impurities and related substances will be monitored in later validation studies.

During product development there may be optimization of the manufacturing process ranging from minor adjustments to a specific step to extensive process modifications. When developing a manufacturing process, operators must understand how each step in the process affects the impurity profile of the drug. Process optimization can be evaluated only if the purity and impurity profile of the drug are known. To determine the type and level of impurities, adequate method development and reference standard qualification should be completed by the end of the Phase 2 program. Full characterization is not always performed, but the purity of the desired product and relative levels of each impurity should be identified and provisional drug substance acceptance criteria should be established. Although in-process controls are still in development, based on the manufacturing history there should be some identified control points in each unit operation to ensure the product will meet the tentative limits in the specifications. Typical control points include input and output parameters that affect whether the intermediate can be processed in subsequent steps.

As a general rule to successfully validate a manufacturing process, the following steps should be performed by the end of the Phase 2 studies: (1) Appropriately scale up the manufacturing process, and minimize any significant process changes that could produce a drug product with characteristics outside of the clinically desired experience; (2) establish operating ranges (input variables) and product quality attributes (output variables) for each manufacturing step; (3) identify critical control parameters and establish in-process controls; and (4) conduct prevalidation runs or qualification trials. Each of these categories is described in detail below.

Manufacturing Scale-Up and Laboratory Runs

By the end of the Phase 2 studies, the commercial manufacturing process should be completely developed. Significant process changes should be minimized unless the change provides an improvement to the quality of the product, significantly reduces the cost of production, improves the robustness and/or reduces the variability of the process, or facilitates transfer to the commercial plant. Small-scale studies typically are performed prior to or concurrently with the production scale up. Small-scale studies are crucial in determining process performance characteristics because evaluating parameters for each unit operation at full scale is extremely costly and time consuming. Characterization of the process using a scaled-down version of the commercial process involves varying process parameters for each manufacturing step and assessing the impact on product quality and process performance. The results of these studies typically are used to support the in-process controls for each manufacturing step, identify and/or verify critical operating parameters, and determine the capability of the overall process. Product comparability studies should bridge the pre- and post-change products.

Establish Operating Ranges and Product Quality Attributes

Operating parameters with defined ranges and intermediate quality attributes for each manufacturing step should be defined. This can be determined by establishing a Proven Acceptable Range (PAR). The PAR includes the upper and lower tolerances for each control step based on a review of previous laboratory and developmental batch data. Determining the PAR for each process parameter can be performed using a process characterization document. This document summarizes the previous manufacturing history, including process conditions, equipment operating ranges, quality of intermediates, quality of raw materials, equipment list and qualification studies, intermediate holds, stability data, and equipment cleaning validation. An added benefit for a comprehensive process characterization document is that it can be used to justify the quality of an intermediate when a manufacturing deviation occurs during commercial manufacturing if a specific process parameter falls outside an acceptable range.

Critical Control Parameters

Once the process characterization document is assembled, the critical control parameters should be identified, and in-process controls should be established. For all control parameters once the upper and lower limits have been defined, the set point typically is operated in the middle of the range. In an early Phase 2 program, in-process control testing of intermediates does not need acceptance criteria for all tests; however, assessing the quality of intermediates helps to identify operating parameters that may affect product quality attributes. If levels of impurities decline or product-related substances are consistently removed and testing is performed to establish levels at specific steps, removal of certain in-process testing and/or exclusion in the drug substance and/or drug product specifications may be justified.

For well-established manufacturing steps such as sterile filtration and lyophilization, standard industry practice can be used to identify critical process parameters. In other cases, the determination of parameters deemed critical or noncritical may not be easily identifiable. Manufacturing steps that have a large number of variables are especially problematic; the same is true when a product quality attribute is a function of two or more variables. Stress studies (e.g., effect of pH, time/temperature, H_2O_2) on product and/or intermediates can suggest parameters that may or

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may not be critical in a given manufacturing step. In laboratory-scale studies, a design of experiment (DOE) approach can be very useful in optimizing processes and identifying critical parameters or critical combinations of parameters in a given manufacturing step or process. Critical and noncritical parameters are identified/verified by a qualified laboratory-scale version of the commercial process. Determining the ranges to evaluate in a scaled-down study depends on the parameter. For example, in a chromatography step if the maximum column load is 10 mg of product per mL of resin and acceptable results are obtained, testing at ranges below 10 mg/mL is not necessary. Other parameter testing usually is performed over a range centered on but at least three times larger than the normal operating range. For example, if a normal operating temperature range for a manufacturing step is ±3 °C with a target temperature of 30 °C (27–33 °C) studies over a range of 21–39 °C could be used to determine if temperature is critical in a given manufacturing step.

The definition of a critical process parameter (CPP) is a parameter for which the PAR is ≤2 times the Normal Operating Range (NOR). Temperature in the example above would be a CPP if the process failed to produce an acceptable product when operated between 34 and 36 °C. Evaluation of several variables operating at the extreme of the operating ranges can help identify optimum operating conditions and determine when failures are likely to occur. It is important to have adequate statistical analysis when two or more variables are evaluated. Scaled-down studies also can be used to support process changes during development and can identify parameters that lead to process variability. The suitability of manufacturing steps, parameters, and processes also can be analyzed using a six-sigma approach to determine Cpk (process capability index), principal component analysis (PCA), or partial least squares (PLS) analysis. A Cpk value of less than 1.33 usually means a process is not capable of reproducibly yielding a quality product.

Trials

Manufacturing trial batches should be produced at the commercial scale prior to execution of the process validation study to ensure that any process parameter changes resulting from scale up are appropriate. The production of these trial batches also serves an important role in ensuring that process analytical technologies utilized to monitor and/or control the process are functioning in accordance with predetermined design criteria and are suitable for their intended use. Phase 2 is the time to make any corrections or changes in the process in the event that the data collected in the small-scale study do not directly transfer to the full-scale process. Manufacturing trials generally are approached by assessing the process in stages: upstream—fermentation, midstream—isolation/purification of protein, and downstream—modification/derivatization of protein. Operating ranges generally are tighter than the acceptable ranges to build ruggedness into the process.

PHASE 3

Prerequisites to Process Validation

The purpose of the process validation study is to confirm, by rational experimental design, that the manufacturing process will reliably produce acceptable product. Characterization of the process and the application of process analytical technologies (PAT) to the intended commercial process provide a high level of process understanding and control capability, thereby providing additional assurance that the process will reliably produce acceptable product. A number of activities must be completed prior to the start of the prospective validation study for the commercial-scale drug substance and drug product manufacturing process. Completion of these activities is fundamental to managing the risks associated with undertaking the process-validation study. The following prerequisites should be completed prior to initiating the process qualification batches:

1. Quality Control Unit

Quality systems must be established and operational as prescribed by applicable current Good Manufacturing Practices (cGMP) e.g., ICH Q7A (*3*) and 21 *CFR* Parts 210 and 211.

2. Equipment and Facility Qualification

Qualification activities must be completed for all equipment, utilities, and the manufacturing facility used in the production and testing of the drug substance and drug product. Appropriate references should be consulted for guidance pertaining to these activities.

3. Method Validation

Analytical procedures associated with testing raw materials, product intermediates, drug substance, and drug product must be fully validated in accordance with the requirements set forth in ICH Q2A (*4*), Q2B (*5*), and applicable compendia. Analytical systems associated with at-line, on-line, or in-line process analysis should be validated to ensure that they are suitable for their intended use.

4. Raw Materials

Quality attributes for raw materials used in the drug substance and drug product manufacturing process must be identified to support qualification activities. An appropriate quality system and/or testing of raw materials to predetermined acceptance criteria are necessary to demonstrate that raw materials are suitable for their intended use.

5. Validation Master Plan (VMP)

A VMP is a document that provides an overview of all activities associated with the process validation study. The VMP serves as the conceptual framework that ensures an integrated systems approach is incorporated into the validation study. This plan should contain or provide reference to the documents associated with the qualification activities discussed above. The VMP serves as the repository for

the preapproved process validation protocol(s), detailed validation report(s) containing the data, and conclusions obtained from the study. The VMP also makes references to studies in the process characterization document.

6. Process Validation Protocol

The Process Validation Protocol contains a summary of the intended commercial-scale manufacturing processes for drug substance and drug product. The purpose of individual processing steps should be stated and supported by data provided in the Process Characterization Document. Specifications for process intermediates, drug substance, and drug product are established in accordance with the requirements set forth in ICH Q6B (*6*). The body of knowledge obtained during process development and characterization activities is used to establish predetermined acceptance criteria for critical process parameters, criteria for forward processing of intermediates (in-process controls), and to justify noncritical parameters for each unit operation. Additional product characterization tests and associated acceptance criteria should be considered in order to provide additional assurance that the process reliably produces acceptable product. The Process Validation Protocol also should address whether monitoring of process- and product-related impurities will be performed as part of quality control testing (in-process control or drug substance specifications) or whether validated removal will be used to support elimination of testing in the drug substance or drug product specification. Product- and process-related impurities include, but are not limited to, host cell DNA, cell culture components (antibiotics, chemical inducing agents), endotoxins, leachates from chromatographic matrices, and other materials introduced during processing. The use of process validation to meet specification requirements for an impurity is based on the levels in the product used in the clinical studies and the clinical consequences.

Stability protocols containing predetermined acceptance criteria for stability-indicating product quality attributes are developed and included in the Process Validation Protocol. These protocols are intended to support the establishment of drug substance process intermediate hold times and drug substance and drug product expiration dates. Protocols are developed in accordance with the requirements set forth in applicable ICH Q1 stability guidelines.

Critical process parameters, in-process controls, in-process specifications, release specifications, and additional testing requirements serve as the basis for the Process Validation Protocol for batches produced at commercial scale. Performance of these runs qualifies the manufacturing process. The criteria for these runs also serve as the basis for parameters that will be trended and reviewed on a periodic basis over the life of the product. All these components together define Process Validation of the drug substance and drug product. Using the defined process, technicians prepare a series of production batches under routine conditions. The identified batches are tested in accordance with the predetermined analytical procedures described in the Process Validation Protocol. The results from these tests are compared to the predetermined acceptance criteria provided in the protocol. It is generally considered acceptable that three consecutive batches produced within the predetermined acceptance criteria constitute a validation of the process. It is important to note that batches intended for commercial sale must be produced at the intended manufacturing scale.

A departure from the acceptance criteria contained in the validation protocol explicitly concludes that the process has not been validated. Departures must be investigated in accordance with established procedures. Causal factors should be identified and remedial actions implemented prior to the initiation of additional validation studies.

MAINTENANCE OF THE VALIDATED STATE

Once the manufacturing process has been successfully transferred and validated for commercial production, the process must be maintained in a validated state. This requires active stewardship and involves not only manufacturing site management but also technical services and quality. On an annual basis, process data from the last year should be reviewed to determine whether the process as validated is still performing to expectations. This annual review should consider such data as deviation history (number, type, by manufacturing step, corrective actions taken, etc.), rejected lots and the basis for rejection, product complaints, recalls, and adverse event data. The latter data may not provide any clear signal; however, for some product types (e.g., parenterals) certain adverse events can signal possible manufacturing issues (e.g., injection site abscess). All change controls should be assessed to determine if the number and extent of changes warrant possible revalidation. Trend analysis should be conducted for all in-process and final lot data. Stability data should be compared against the registration commitments to determine if the degradation rates and impurities profiles are consistent. When technically feasible, the application of PAT for continuous process control is encouraged. Evaluation of PAT data over time can provide powerful insights regarding the maintenance of the validated state.

If upon completion of an annual review, there appears to be a change in the performance of the process, the manufacturer should consider additional technical evaluations to get to the root cause of performance change. Ultimately, if performance data are sufficiently different from the process as originally validated, then revalidation may be needed. The manufacturer may consider a planned revalidation every 3–5 years as a matter of good stewardship to demonstrate that the process is still in control, capable, and compliant with regulatory commitments.

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The Use of Relative Response Factors to Determine Impurities

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ABSTRACT Relative Response Factor is a critical analytical parameter widely used in chromatographic procedures to control impurities in drug substances and dosage forms. Lacking a standardized approach, manufacturers develop case-by-case solutions, which reduces the likelihood "of ensuring that measurements made at different times, by different analysts, or with different methods can be confidently compared"—a goal of sound metrology *(1).* Inconsistencies also exist in the *USP–NF* monographs and, in a few cases, even within the same monograph. The use of the parameter is left open to the interpretation of the monograph user, which may lead to the possibility of misinterpretation. This *Stimuli* article reviews approaches to Relative Response Factors, elucidates their nomenclature and applications, and proposes ways in which they can be standardized throughout *USP–NF* and *PF.*

INTRODUCTION

Impurities have drawn significant attention recently as critical quality attributes for drug substances and dosage forms. This has been reflected in the International Conference on Harmonization (ICH) Q3 guidelines, Food and Drug Administration (FDA) guidance documents, and the USP *Guideline for Submission of Requests for Revision to USP–NF.*

Optimally, official USP Reference Standards for impurities should be relied on in the execution of a monograph's *Impurity* test. In this regard, USP offers more than 300 reference standards for impurities and is working to offer many more. However, official USP Reference Standards for impurities may not be available for a number of reasons, including lack of donation, difficulty in isolation, and difficulty in synthesis. Where an appropriate reference standard(s) is not available, a USP monograph, relying on instrumental techniques (e.g., gas or liquid chromatography), may help control the impurities in a compendial article through reliance on the Relative Response Factor (RRF) approach, usually in conjunction with an official USP Reference Standard for the corresponding drug substance. The approach allows expressing the mass of an impurity in terms of the mass of its corresponding drug substance, e.g., a specified impurity is present in the article at a mass of 0.1% of the mass of the drug substance. This correlation between the response factor (RF) of the impurity or impurities and the drug substance must be documented in the validation data submitted by a Sponsor in a Request for Revision.

An RRF value, which is specific to a given set of experimental conditions, compares the instrumental responses of the impurity and the drug substance reference standard and is incorporated into a formula as a means to correct for differences in detector response. An additional valuable parameter in the *Impurity* test procedure is the Relative Retention Time (RRT). *USP–NF* monographs often use RRTs and RRFs to identify and control impurities.

Approximately 120 of the monographs published in *USP 28–NF 23* and in *Pharmacopeial Forum (PF)* to Vol. 30, No. 6 (see *Table 1* following References) use an RRF for the determination of impurities. The remainder either do not test for impurities or use a peak area approach. At present, *USP–NF* does not have an official definition or standard for the use of RRF, nor do FDA guidances and ICH guidelines. USP monographs also present at times differing approaches and nomenclature. A review of *USP–NF* monographs shows that the same parameter is termed differently in different monographs (*Table 1*). Some of the monographs use the term *Response Factor,* some use the term *Relative Response Factor,* and others use *Correction Factor.* Furthermore, in some formulas for calculation of percent impurity, the term is used in the numerator and in others it is used in the denominator. In addition, the number of decimal places used to express the RRF differs among monographs from one to four decimal places. A few examples will illustrate these issues.

Example 1

The Metrifonate monograph states:

> Calculate the percentage of each impurity taken by the formula:
>
> $$100F(r_i / r_S),$$
>
> in which F is a response factor, being 0.38 for the desmethylmetrifonate peak, if present at a retention time of 0.5 relative to that of Metrifonate, 0.03 for the dichlorvos peak, if present, at a retention time of 1.9 relative to that of Metrifonate, and 1.0 for any other impurity . . .

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In this example, the term *F* is denoted as "response factor" and is used to mean the same parameter as RRF in other monographs. The term is used in the numerator in the formula to calculate the percentage of each impurity in the drug substance. The RF values are expressed to two decimal places when they are less than 1.0 and to one decimal place when it is equal to 1.0. However, the value of the RF for the dichlorvos peak is extremely low, 0.03, which could result in underestimation of the impurity (discussed in greater detail later in this article).

Example 2

The Oxandrolone monograph proposed in *PF* 31(1) (pp. 64–67) states:

> Calculate the percentage of each impurity in the portion of Oxandrolone taken by the formula:
>
> $$500(1/F)(C/W)(r_i / r_S),$$
>
> in which *C* is the concentration . . . *F* is the relative response factor and is equal to . . .

In this monograph the term *F* is denoted as the RRF and is used in the same sense as RF in Example 1. In contrast to Example 1, here the term appears in the denominator in the formula. As in Example 1, the values of the RRF in this monograph are given to two decimal places if they are below 1.0 and to one decimal place when they are $\geq$1.0 (not shown).

Example 3

The Clarithromycin monograph indicates:

> Calculate the percentage of each impurity in the Clarithromycin taken by the formula:
>
> $$50(C_C/W)(r_i F/ r_C)P,$$
>
> in which C_C is the concentration . . . *F* is 1.0, or correction factor of 0.27, and 0.15 applied to the responses for peaks at relative retention times in relation to that of clarithromycin . . .

In this monograph, the term *F* is called "correction factor" but is used in the same sense as "response factor" in Example 1 and "relative response factor" in Example 2. Note that it appears in the numerator in the formula. As in the two examples above, the values of *F* are expressed to two decimal places when the values are less than 1.0 and to one decimal place when the value is equal to 1.0 in this monograph.

Example 4

The Sevoflurane monograph indicates:

> [For] other known impurities . . . their amounts present are determined using their respective relative response factors (*Table 2*) by the formula:
>
> $$FC_{SME–std}\ (r_i / r_{SME–std})$$
>
> Use the relative response factor of SME [USP Sevomethyl Ether RS] to calculate the unknown impurities. *F* is the relative response factor of the known impurity not present in the *Standard solution* . . .

Table 2

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

In this example, the term *F* is called the "relative response factor." It appears in the numerator in the formula. Also, the values of *F* are expressed to four decimal places, except for Sevomethyl ether and "Unknown impurities," for which the values are given as 1 (without any decimal place). Also, the values of the RRT of four of the impurities are given to two decimal places, but that of Sevomethyl ether is expressed without any decimal place.

Example 5

The Fluvastatin Sodium monograph indicates:

> Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin . . .
>
> $$100F(C_S / C_T)(r_{i(305)} / r_{S(305)})$$
>
> in which *F* is the relative response factor as listed in *Table 3*. [NOTE—Use *F* equal to 1.0 for unknown impurities]. . .

Table 3

Impurity	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
Fluvastatin *N*-ethyl analog	0.7	0.9	0.1
Fluvastatin anti-isomer	1.2	1.0	0.8
3-Hydroxy-5-keto fluvastatin	1.5	0.037	0.1
3-Keto-5-hydroxy fluvastatin	1.6	1.6	0.1
Fluvastatin hydroxy-diene	2.0	1.1	0.1
Fluvastatin short-chain aldehyde	3.0	0.7	0.1
Fluvastatin *t*-butyl ester	3.4	1.1	0.2

In this example, the term *F* is called "relative response factor" and is used in the numerator in the formula. The values are given to one decimal place except for the impurity 3, for which it is given to three decimal places. Also, the value of impurity 3 is extremely small. In addition, the values of the RRT are given to one decimal place, but in Example 4 the values of the RRT of four of the impurities are given to two decimal places.

DISCUSSION

The inconsistencies in different *USP–NF* monographs regarding terms used for RRF, how it is used in the formulas, and the number of decimal places to which the values are expressed can be traced primarily to the different approaches adopted by different Sponsors of Requests for Revision. The RRF is placed in the numerator or in the denominator in the formula for calculating percent impurity depending on how it is defined. *Appendix A* shows that the term should be in the numerator if it is defined as the RF of the drug substance divided by that of the impurity. Conversely, it should be in the denominator if it is defined as the ratio of the RF of an impurity to that of the drug substance. That is why the formulas contain RRF in the denominator in many monographs and in the numerator in many others, depending upon how the company that submitted the monograph defined it.

One can argue that whether the term is in the numerator or in the denominator may not be an issue if a monograph indicates how it is defined or calculated. However, current monographs provide values only for the RRF—but, generally, give no details about its calculation. Thus, it is left open to judgment and interpretation by the user of the monograph (other than the submitter) with the consequent possibility of misinterpretation. Furthermore, the fact that RRF is used differently in formulas in different monographs is contrary to the practices of standardization to which USP is committed. As an example, consider that a monograph indicates that the RRF of an impurity is 0.65. Because the monograph does not say how it is defined or calculated, this could be the peak response of the impurity divided by the peak response of an equal amount of the drug substance—or it could be the peak response of the drug substance divided by the peak response of an equal amount of the impurity. The monograph Sponsor knows how it was calculated, but other users are not informed, raising the possibility of differing application and an incorrect result.

USP also does not have any requirement regarding the range over which an RRF can be used. The *British Pharmacopoeia* requires that an RRF be used only if it is in the range 0.2–5.0 *(2).* It is difficult to accept such a "one size fits all" approach without appropriate scientific justification. The acceptable value of the RRF should depend upon the analytical parameters of the *Impurity* test procedure, including the linear range, accuracy, and the robustness. If an RRF value is calculated based on the data obtained outside the linear ranges of the impurity and the drug substance (either below the Limits of Quantitation or above the linear range determined during validation), the impurity percentage is likely to be underestimated. Such an approach is inconsistent with the requirements of the ICH Q3A(R) guideline *(3),* which states,

> *"The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated"* (emphasis added).

In addition, USP does not indicate when the RRF can be rounded off to 1.0. Data submitted to USP show the current practice varies widely. Some Sponsors round off the RRF values to 1.0 when they are in the range 0.80–1.2, some do so when they are in the range 0.90–1.1, and others do so when they are in the range 0.95–1.05. The *European Pharmacopoeia* requires that, if the value of the RRF is different from 0.8–1.2, it should be included in the monographs *(4).*

PROPOSAL

In order to address the issues discussed above and in the interest of developing a uniform and consistent standard that can apply to all *USP–NF* monographs, this *Stimuli* article provides a proposal for a consistent compendial approach regarding the use of RRF to control impurities in an article. The approach would be part of revision of appropriate General Chapters and Monographs.

1. Use the symbol *F* to designate the RRF consistently.
2. Define the RRF of an impurity as the ratio of the peak response of the impurity to that of an equal mass of the drug substance. That is,

$$F = r_i / r_U,$$

   in which r_i and r_U are the peak responses of equal masses of the impurity, *i,* and the drug substance, *U,* respectively.
3. Define the term RF of an analyte as the peak response per unit mass of the analyte.
4. Include the definitions of RRF and RF in the Glossary section of General Chapter ⟨621⟩ *Chromatography* and revise General Chapter ⟨1225⟩ *Validation of Compendial Methods,* as appropriate.
5. Eliminate terms such as Correction Factor and Response Factor from *USP–NF* monographs, and replace them with RRF where appropriate, that is, where evaluations of the data submitted together with the monograph submission show that the terms Correction Factor or Response Factor were used to mean the same thing as the RRF. However, where such terms are used to mean different parameters—for example, the term RF is used to mean the peak response per unit mass of the analyte—they will be retained.

6. Use the RRF for impurity measurement only if the value is accurately determined over the linear range of the procedure for the impurity and the drug substance. This requirement will be included in General Chapter ⟨621⟩.
7. State the RRF values in monographs to one decimal place if it is equal to or greater than 1.0 and to two decimal places if it is less than 1.0. That is, the RRF value will be expressed to two significant digits. The ICH Q3A(R) guideline (*2*) indicates that the impurity results should be reported to one decimal place if they are at or above 1.0 and to two decimal places if they are below 1.0. Thus, this proposal will make the *USP–NF* requirement consistent with the ICH Q3A(R) guideline. This requirement will be included in General Chapter ⟨621⟩.
8. The RRF values can be rounded off to 1.0 in *USP–NF* monographs if they are in the range 0.8–1.2, calculated per the definition above. This requirement will be included in General Chapter ⟨621⟩.
9. Revise the USP Guideline to include recommendations to Sponsors of Requests for Revision when the RF and RRF approaches are used in compendial articles.

Implementation Plan

1. General Chapter ⟨621⟩ *Chromatography* will be revised to include the changes described above, and the proposed revision will be published in *PF* for public review and comment and adopted by the usual USP procedures.
2. *Table 1* shows a list of monographs affected by this proposal. Each monograph in *Table 1* will be evaluated using the data that were submitted to USP as part of the sponsor's Request for Revision to determine if the RRF values, the formula(s), and other information in the monograph are consistent with the proposals outlined above. If necessary, monographs will be revised to make them consistent with the current proposals and then will be published in *PF* for public review and comment. This may include recalculating the RRF values based on the data submitted to USP, changing the number of decimal places of the RRF values, rewriting the formula(s), and/or changing the terminology and symbol, on an as-needed basis. The revisions will be adopted through the appropriate USP procedures.
3. Proposal 8 above will be implemented prospectively (only for new monographs).
4. When adequate data are not available, USP Scientific Liaisons will contact Sponsors for the data, and revisions will be made based on subsequent review of the data. If the requested data cannot be obtained, necessary data may be generated by the USP Research and Development Laboratory.
5. The implementation of the revisions to current monographs may be delayed to allow sufficient time for manufacturers to make necessary changes in their internal documents and to report amendments to FDA.

CONCLUSIONS

RRF is a common parameter frequently used in many chromatographic procedures. The parameter is particularly critical for quantitative or limit tests for impurities because in many cases the corresponding reference standards are not available. To date *USP–NF* does not have standards, including a definition, for this parameter. Consequently, the terminology, number of decimal places of the values, and the formulas for calculating percent impurities are different in different monographs. The emphasis on impurity testing and control is an outcome of the ICH Q3 guidelines. Approximately 120 of the monographs published in *USP 28–NF 23* and up to *PF* Vol. 30 No. 6 (*Table 1*) use RRF for impurity determination, although inconsistent terminology appears among them (e.g., Relative Response Factor vs. Response Factor vs. Correction Factor). Many of them are consistent with the proposals advocated above. Thus, if the proposals are implemented now, a relatively small number of monographs will need revision, and the standards can be applied to all incoming monographs. The number of monographs that involve RRF is expected to grow rapidly due to the current emphasis on impurity control.

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Table 1. Monographs that use Relative Response Factor (RRF), Response Factor (RF), or Correction Factor (CF) for measurement of impurities

Monograph*	Terminology in Monographs	Included in the Formula as
Allopurinol (*PF*)	RRF	Numerator
Anecortave Acetate (*PF*)	RRF	Numerator
Anecortave Acetate Injectable Suspension (*PF*)	RRF	Numerator
Atovaquone Oral Suspension	RF	Denominator
Betahistine Hydrochloride (*PF*)	RF	Numerator
Bethanechol Chloride	RRF	Numerator
Bethanechol Chloride Tablets	RRF	Numerator
Bisoprolol Fumarate and Hydrochlorothiazide Tablets	RF	Denominator
Bromocriptine Mesylate	RRF	Denominator
Bupropion Hydrochloride	RRF	Numerator
Bupropion Hydrochloride Extended-Release Tablets	RRF	Numerator
Caffeine Citrate Injection	RRF	Numerator
Caffeine Citrate Oral Solution	RRF	Numerator
Caffeine Injection (*PF*)	RRF	Numerator
Caffeine Oral Solution (*PF*)	RRF	Numerator
Ciprofloxacin Injection	RRF	Numerator
Clarithromycin	CF	Numerator
Clindamycin Phosphate (*PF*)	RF	Denominator
Clonazepam	RRF	Numerator
Clonazepam Tablets	RRF	Numerator
Collodion	RRF†	—
Cytarabine	RRF	Denominator
Desogestrel and Ethinyl Estradiol Tablets (*PF*)	RRF	Denominator
Dinoprost Tromethamine	RRF	Numerator
Dinoprostone	RRF	Denominator
Doxazosin Mesylate (*PF*)	RF	Numerator
Echinacea angustifolia	RF	Numerator
Echinacea pallida	RF	Numerator
Echinacea purpurea Root	RF	Numerator
Echinacea purpurea Aerial Parts	RF	Numerator
Enalapril Maleate Tablets (*PF*)	RRF	Numerator
Erythromycin	RF	Denominator
Erythromycin Ethylsuccinate	RF	Denominator
Erythromycin Stearate	RF	Denominator
Ethotoin	RF	Denominator
Famotidine Tablets	RRF	Denominator
Fenoldopam Mesylate	RF	Numerator
Fexofenadine Hydrochloride (*PF*)	RF	Numerator
Fish Oil Rich in Omega-3 Acids *(PF*)	RF	Numerator
Fludarabine Phosphate	RRF	Numerator
Fludarabine Phosphate for Injection	RRF	Numerator
Flumazenil (*PF*)	RRF	Denominator
Flutamide	RRF	Numerator
Fluvastatin Sodium (*PF*)	RRF	Numerator
Fluvastatin Capsules (*PF*)	RRF	Numerator
Fluvoxamine Maleate (*PF*)	RF	Numerator
Fluvoxamine Maleate Tablets (*PF*)	RF	Numerator
Gabapentin (*PF*)	RRF	Numerator
Gadoteridol	RRF	Numerator
Glyceryl Monostearate	RF	Numerator
Guaifenesin	RF	Numerator

Table 1. Monographs that use Relative Response Factor (RRF), Response Factor (RF), or Correction Factor (CF) for measurement of impurities *(Continued)*

Monograph*	Terminology in Monographs	Included in the Formula as
Hydrochlorothiazide	RF‡	Both in numerator and denominator
Hydrocodone Bitartrate	RRF	Numerator
Hypromellose	RRF‡	Numerator
Indinavir Sulfate Capsules (*PF*)	RRF	Numerator
Ketorolac Tromethamine	RF	Numerator
Lansoprazole (*PF*)	RRF	Numerator
Levodopa	CF	Numerator
Levodopa Tablets (*PF)*	RRF	Numerator
Loratadine	RRF	Denominator
Lovastatin	RF	Numerator
Mephenytoin	RRF	Numerator
Mephenytoin Tablets	RRF	Numerator
Methylcellulose	RRF§	Numerator
Metrifonate	RF	Numerator
Mirtazapine (*PF*)	RRF	Numerator
Mirtazapine Tablets (*PF*)	RRF	Numerator
Modafinil (*PF*)	RRF	Denominator
Modafinil Tablets (*PF)*	RRF	Denominator
Morphine Sulfate Extended-Release Capsules	RRF	Numerator
Nabumetone	RRF	Numerator
Naltrexone Hydrochloride	RRF	Numerator
Naratriptan Hydrochloride	RRF	Denominator
Naratriptan Tablets	RRF	Denominator
Nevirapine	RRF	Denominator
Norgestimate	RRF	Denominator
Norgestimate and Ethinyl Estradiol Tablets (*PF*)	RRF	Numerator
Ofloxacin	RF	Numerator
Omeprazol Delayed-Release Capsules	RRF	Denominator
Ondansetron Hydrochloride	RRF	Denominator
Ondansetron Orally Disintegrating Tablets (*PF*)	RRF	Denominator
Ondansetron Oral Solution (*PF*)	RRF	Numerator
Orphenadrine Citrate	RRF	Numerator
Orphenadrine Citrate Injection	RRF	Numerator
Oxandrolone (*PF*)	RRF	Numerator
Oxaprozin	RRF	Numerator
Oxybutynin Chloride (*PF*)	RRF	Denominator
Paclitaxel	RRF	Numerator
Pentobarbital	RRF	Denominator
Pentobarbital Sodium	RRF	Denominator
Piperacillin	RRF	Numerator
Piperacillin for Injection	RRF	Numerator
Piperacillin Sodium	RRF	Numerator
Powdered *Echinacea angustifolia* Extract	RF	Numerator
Powdered *Echinacea pallida* Extract	RF	Numerator
Powdered *Echinacea purpurea* Extract	RF	Numerator
Powdered St. John's Wort Extract	RF	Denominator
Propofol	RF	Denominator
Ramipril	RRF	Numerator
Repaglinide	RF	Numerator
Saquinavir Capsules	RF	Numerator

Table 1. Monographs that use Relative Response Factor (RRF), Response Factor (RF), or Correction Factor (CF) for measurement of impurities *(Continued)*

Monograph*	Terminology in Monographs	Included in the Formula as
Saquinavir Mesylate	RF	Numerator
Sevoflurane (*PF*)	RRF§	Numerator
St. John's Wort	RF	Denominator
Succinylcholine Chloride	RF	Numerator
Sumatriptan Nasal Spray (*PF*)	RRF	Numerator
Stavudine (*PF*)	RRF	Numerator
Tiagabine Hydrochloride	RRF	Numerator
Tocopherols Excipient	RRF	Denominator
Tolazamide	RRF	Numerator
Tolcapone (*PF*)	RRF	Numerator
Topiramate (*PF*)#	RRF/CF	Denominator/Numerator
Trimethoprim	RRF	Both in numerator and denominator
Vitamin E	RRF	Denominator
Xylazine	RF	Numerator
Zidovudine Tablets	RRF	Numerator
Zileuton	RRF	Numerator

* (*PF*) means that the monographs currently are published in *PF* as proposals.
† In the Collodion monograph the term RRF is used to mean the ratio of the concentration of C_2H_5OH to the area ratio of alcohol to acetone in the respective standard preparations. The use of the term in this sense is unique and is different from the meaning of the term RRF elsewhere in *USP–NF*.
‡ The definition of RF is given in the monograph and is consistent with the definition proposed in the current article.
§ The calculations of RRF/RF are included in the monographs.
# The Topiramate monograph uses the term RRF in the *Related compounds* test and uses the term in the denominator in the formula. However, in the *Limit of sulfamate and sulfate* test it uses the term CF and includes it in the numerator in the formula.

APPENDIX A

F is the RRF of an impurity, *i,* with respect to the drug substance, *U,* and is defined as the ratio of the peak response of the impurity to that of an equal mass of the drug substance.

So, $F = r_i / r_U$, where r_i is the peak response of unit mass of the impurity peak, and r_U is the peak response of an equal mass of the drug substance peak.

If the sample contains x_i mass of impurity and C_U mass of drug substance (expressed in the same unit), then,

$x_i r_i = R_i$, where R_i is the peak response of the impurity peak in the sample and

$C_U r_U = R_U$, where R_U is the peak response of the drug substance peak in the sample.

Hence, $(x_i r_i)/C_U r_U = R_i / R_U$.

That is, $(x_i F)/C_U = R_i / R_U$.

Therefore, $x_i / C_U = (1/F)(R_i / R_U) = (1/F)(R_i / R_S)(C_S / C_U)$, because $C_U / C_S = R_U / R_S$ or $R_U = (C_U / C_S)R_S$.

Thus, Percent Impurity $= 100x_i / C_U = (100/F)(R_i / R_S)(C_S / C_U)$.

On the other hand, if *F* is the RRF of an impurity, *i,* peak with respect to the drug substance, *U,* peak and is defined as the ratio of the peak response of the drug substance to that of an equal amount of the impurity, then,

$$\text{Percent Impurity} = 100x_i / C_U = 100F(R_i / R_S)(C_S / C_U).$$

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
2005 USP DICTIONARY SUPPLEMENT 1

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

Revisions of United States Adopted Names (USAN)

The following is a revision of an existing United States Adopted Name (USAN).

Canfosfamide Hydrochloride

Change the manufacturer to read:

(Telik)

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.

Proposed International Nonproprietary Names

The following 57 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. 18, No. 4, 2004.

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
Ancriviroc	*Antiviral*
Artemifone	*Antimalarial*
Atilmotin	*Digestive agent*
Avanafil	*Vasodilator*
Balicatib	*Cathepsin K inhibitor*
Becatecarin	*Antineoplastic*
Becocalcidiol	*Vitamin D analogue*
Bemotrizinol	*Sunscreen*
Besilesomab	*Radioimmunodiagnostic agent*
Bisoctrizole	*Sunscreen*
Canfosfamide	*Antineoplastic*
Ceftobiprole	*Antibiotic*
Ceftobiprole medocaril	*Antibiotic*
Centredekin besudotox	*Antineoplastic*
Davasaicin	*Topical analgesic*
Deferitrin	*Iron chelator*
Delmitide	*Immunomodulator*
Deutolperisone	*Muscle relaxant*
Efipladib	*Cytosolic phospholipase A2 inhibitor*
Elomotecan	*Antineoplastic*
Embeconazole	*Antifungal*
Epoetin zeta	*Antianaemic*
Eritoran	*Bacterial lipopolysaccharide receptors antagonist*
Etalocib	*Antineoplastic*
Farampator	*Antipsychotic*
Forodesine	*Antineoplastic*
Galsulfase	*Enzyme*
Glucarpidase	*Enzyme*
Iboctadekin	*Antineoplastic*
Icomucret	*Mucin secretion stimulator*
Inotuzumab ozogamicin	*Antineoplastic*
Isalmadol	*Analgesic*
Ispinesib	*Antineoplastic*
Levotofisopam	*Anxiolytic*
Linaprazan	*Acid pump inhibitor*
Morphine glucuronide	*Analgesic*
Naveglitazar	*Antidiabetic*
Omocianine	*Fluorescent diagnostic contrast agent*
Peliglitazar	*Antidiabetic*
Pemaglitazar	*Antidiabetic*
Perflisobutane	*Ultrasound contrast agent*
Piclozotan	*Serotonin receptor antagonist*
Pralatrexate	*Antineoplastic*
Radotermin	*Growth factor*
Raxibacumab	*Antitoxin*
Rimeporide	*NA+/H+ antiport inhibitor*
Salclobuzic acid	*Pharmaceutical aid*
Saxagliptin	*Antidiabetic*
Seliciclib	*Antineoplastic*
Sugammadex	*Pharmaceutical aid*
Talabostat	*Antineoplastic*
Talactoferrin alfa	*Recombinant human lactoferrin*
Talaglumetad	*Anxiolytic*
Tanogitran	*Antithrombotic*
Tefibazumab	*Antitoxin*
Temsirolimus	*Immunosuppressant*
Thrombomodulin alfa	*Prevention and treatment of thrombosis*

Recommended International Nonproprietary Names

The following 49 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. 18. No. 3, 2004.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Adecatumumab	Doranidazole	Muraglitazar	Sabarubicin
Arformoterol	Ecopladib	Nebentanum	Solabegron
Banoxantrone	Eglumetad	Netupitant	Tadekinig alfa
Batabulin	Enzastaurin	Omigapilum	Tanaproget
Becampanel	Esoxybutynin	Paclitaxel poliglumex	Taneptacogin alfa
Beminafil	Parathyroid hormone	Pasireotide	Taprizosin
Binodenoson	Idursulfase	Pelitrexol	Teduglutide
Certolizumab pegol	Imidafenacin	Pruvanserin	Tocilizumab
Ciluprevir	Lacosamide	Ramelteon	Urtoxazumab
Clazosentan	Lumiliximab	Ranibizumab	Valtorcitabine
Clofarabine	Maropitant	Razaxaban	Vildagliptin
Daglutril	Mubritinib	Rivaroxaban	Zanolimumab
Dextofisopam			

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
Abrextrin Apiclermin Aplicermin Aprexermin Aprextrin Daprexermin Dapiclermin	*Treatment of obesity*
Adarolimus Etosirolimus Tetrazolimus Tetrolimus Tetrosirolimus Tezolimus Tezorolimus Zolimus Zoterolimus	*Antifungal macrolide (drug component of an investigational phosphoryl choline polymer coated eluting stent, currently under evaluation for the prevention of coronary restenosis following stent replacement*
Adfilcon H Alifilcon H Paflufocon D-hemiberfilcon A	*Rigid gas permeable contact lens material with a poly-HEMA soft skirt; Hybrid contact lens material*
Adopanib Hydrochloride Balitanib Hydrochloride Pazopanib Hydrochloride	*Antineoplastic*
Aerofilcon Comfilcon Comfilcon A Elvifilcon A Gomlifilcon A Miplofilcon A Omsifilcon A Oxsilfilcon Pomifilcon A Silfilcon Tepsifilcon A	*Hydrophilic contact lens material*
Altamisate Altarmirsate Ambetisate Amyglybril Amytargam Betamilod Cosamisate Prevamilod Preveglybril Prevetargam Tarlamibril Disodium Zeprotargam Zontargam	*Treatment of mild-to-moderate Alzheimzer's disease, treatment of cerebral amyloid angiopathy (antiamyloidotic)*

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

Suggested USAN	Category
Amyglybril Amytargam Fibramilod Fibritargam Prevamibril Disodium Prevamilod Preveglybril Prosdisate Disodium Zontargam	*Treatment of secondary (AA) amyloidosis*
Apaxabam Apixaban Aprixaban Belaxaban Cinaxaban	*Anticoagulant; antithrombotic*
Avaquizotin Mesylate Avasizotine Mesylate Avazositine Mesylate Tazositine Mesylate Trasizotine Mesylate Trazositine Mesylate Trequizotin Mesylate	*Antidepressant*
Belizumab Crelizumab Lolizumab Ocrelizumab Relizumab Ubelizumab	*Treatment of rheumatoid arthritis*
Betafilcon A Omegafilcon	*Hydrophilic contact lens material*
Bolamevatide Bolatide Disomevatide Lamevatide	*Melanoma peptide vaccine*
Bosatinib Fanditinib Tolatinib	*For use in oncologic treatment*
Brifospofol Disodium Brifosprofol Fospropofol Disodium Prefospofol Disodium Profospofol Disodium Proposfol Phosphate Disodium	*Intravenous sedative-hypnotic solution in conscious sedation for brief surgical and diagnostic procedures*
Brilipladib Corbilipladib Ordilipladib	*Treatment of atherosclerosis*
Cardoxinyl Hydrochloride Hexodinyl Hydrochloride Mefenexane Hydrochloride Nefenakant Nexonokoc	*Treatment of patients with atrial fibrillation and atrial flutter*
Cemlimarev (CEA, MUC-1, vaccinia vaccine) Cemllimarev (multigene vaccinia virus) Cemtulimarev-Alfa Cemtulirev-Alfa	*Treatment of pancreatic cancer; treatment of CEA-bearing cancers*
Cemtulimarev-Beta Cemtulirev-Beta Molimarev (CEA, MUC-1, vaccinia vaccine) Molimarev (multigene vaccinia virus)	*Treatment of pancreatic cancer; treatment of CEA-bearing cancers*
Cetforlimumab Cetirilimumab Cetlalimumab Cetolimumab Citilimumab	*Treatment of cancer*
Darlipladib	*Treatment of atherosclerosis*
Diaplaginin Diaplasginin Diaplastinin Diaplaxtinin	*Treatment of fibrinolytic impairment disease*
Elzydavose Hydrochloride Fabenimose Hydrochloride	*Treatment of Fabry disease*
Emavatide Omatide Omevatide	*Melanoma peptide vaccine*
Esmirtazapine Maleate	*Treatment of moderate to severe vasomotor symptoms associated with menopause*
Goxalipadib Oxalipadib Voxalipadib	*Treatment of atherosclerosis*
Indisulam	*Antineoplastic*
Lusaridone Hydrochloride	*Treatment of schizophrenia*
Melanotide Pamelacron Pamelactron Pamelcortide Pamelcotide Panocortide	*Treatment of sexual dysfunction*
Ologlisec Serglisec Tranoglisec	*Treatment of Type II diabetes mellitus as monotherapy and in combination with other glucose lowering agents*
Pelacriviroc Hydrochloride Pelaviroc Hydrochloride Sirocrivoc Hydrochloride Siroviroc Hydrochloride	*Treatment of HIV infection*
Pradefovir Mesylate Ranofovir Mesylate Remofovir Mesylate	*Antiviral*
Prataxomer Acetate Pratiramer Acetate Tagliramer Acetate	*Treatment of multiple sclerosis and glaucoma*
Reparixin	*Treatment of delayed graft function*

Suggested USAN	Category
Scovavirine Choline Sedovorine Choline	*Treatment of HIV infection*
Ticalizumab Tilolizumab Tradulizumab	*Treatment of B-cell malignancies*
Valategrast	*Treatment of asthma*
Valpreotide Acetate	*Treatment of acute variceal bleeding related to portal hypertension*

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
Abrafibrate Espafibrate Relafibrate	*Treatment of dyslipidemia*
Adarolimus Tezorolimus Zoterolimus	*Antifungal macrolide (drug component of an investigational phosphoryl choline polymer coated eluting stent, currently under evaluation for the prevention of coronary restenosis following stent replacement*
Aliskiren Fumarate	*Treatment of hypertension*
Apaxaban Apixaban Aprixaban	*Anticoagulant; antithrombotic*
Brexanavir Pixanavir Prexanavir	*Treatment of HIV infection*
Casipitant Mesylate Cenapitant Mesylate Crinapitant Mesylate	*Treatment of depression, anxiety, sleep disorders, nausea and vomiting, functional dyspepsia, irritable bowel syndrome, gastroesophageal reflux disease, and overactive bladder disease*
Cilansetrone Hydrochloride	*Treatment of diarrhea-predominant Irritable Bowel Syndrome*
Crelizumab Ocrelizumab	*Treatment of rheumatoid arthritis*
Dapiclermin Daprexermin	*Treatment of obesity*
Denogliptin Tosylate Nalagliptin Tosylate Raligliptin Tosylate	*Treatment of Type II diabetes mellitus*
Diaplaginin Diaplasginin Diaplastinin Diaplaxtinin	*Treatment of fibrinolytic impairment disease*
Elzigalastat Hydrochloride Elzivadose Hydrochloride	*Treatment of Fabry disease*
Entrigapex Rotigapex Rotigapide Rotiregap	*Treatment of ventricular tachycardia or ventricular fibrillation*
Esmirtazapine Maleate	*Treatment of moderate to severe vasomotor symptoms associated with menopause*
Fesoterodine Fumarate	*Treatment of overactive bladder*
Indisulam Indisumide	*Antineoplastic*
Netupitant	*NK1 receptor antagonist*
Pradefovir Mesylate Remofovir	*Synthetic nucleotide antiviral agent*
Sodium Cholate Soy Fatty Acids Sodium Cholate Soy Phasphatidylcholine Soy Posepibex Soyafotaline	*Treatment of patients with Gram-negative sepsis*

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 31(1).

[*Note—This index covers Vol. 31, No. 1, pp. 1–288, Vol. 31, No. 2, pp. 289–669, Vol. 31, No. 3, pp. 671–980*]

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* The *USP–NF* (*USP29–NF24*), 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:

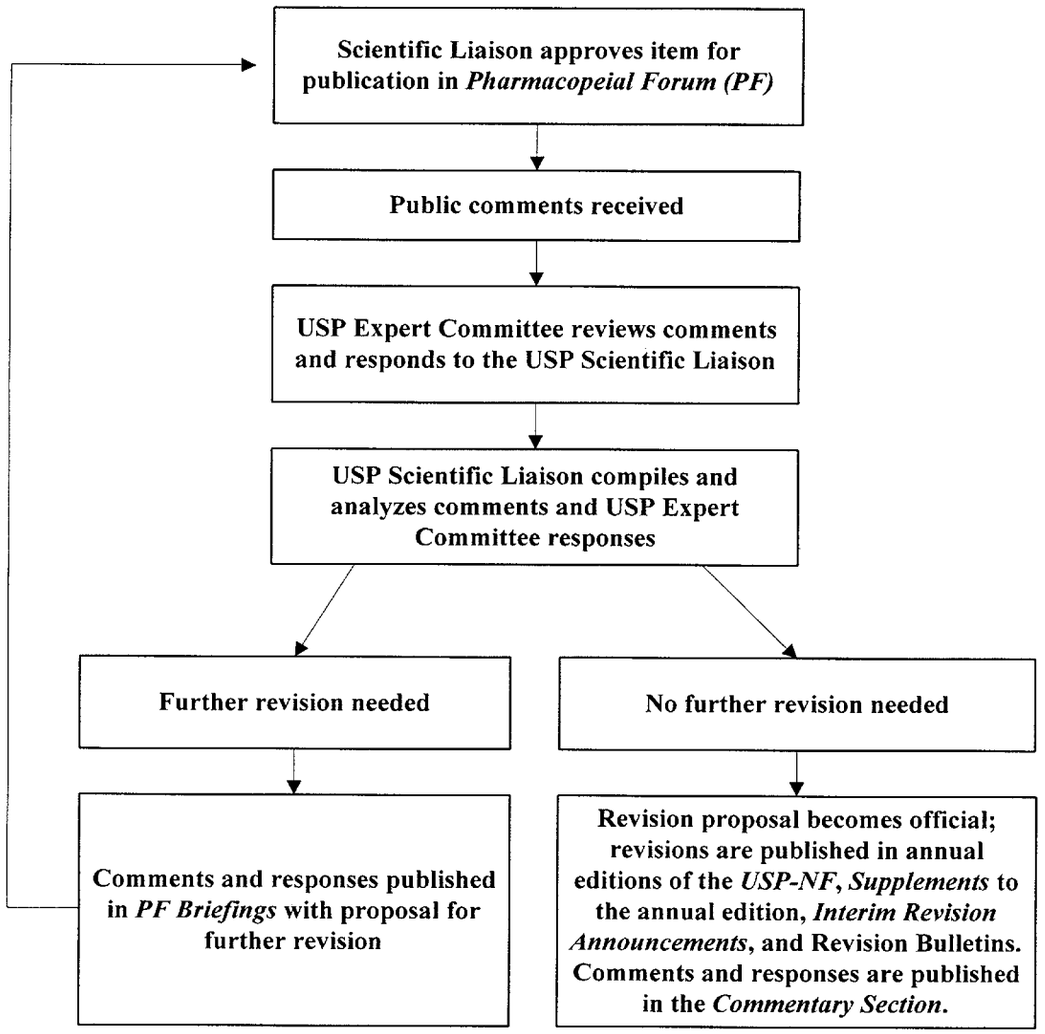
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official 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 *USP-NF* Standards Development



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@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 content of the different sections of *PF* are briefly described below. 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 in the *Guideline for Submitting Requests for Revision to the USP-NF* on the USP website (http://www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP-NF*

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 working 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.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

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
- Where to find 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* 31(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:

2000—2005

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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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 7a—Antibiotics; 7b—Antimicrobials and Antivirals
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

2005—2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell and Gene Therapy
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCRX	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RAD-INFO	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET DRUG	Veterinary Drugs
VET MED INFO	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005-2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

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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.

CALL FOR HIGH PRIORITY MONOGRAPHS FOR DRUG SUBSTANCES AND PRODUCTS, AND EXCIPIENTS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monograph sponsors should consult USP's *Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/standards/revisionguideline/index.html. **For further information, contact Lokesh Bhattacharyya, Ph.D., lb@usp.org.**

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules	Acetaminophen, Clemastine Fumarate and Pseudoephedrine Hydrochloride Tablets
Acetazolamide Extended-Release Capsules	Alatrofloxacin Mesylate	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin	Alfuzosin Tablets	Allopurinol for Injection
Allopurinol Sodium	Alprazolam Extended-Release Tablets	Alprostadil Urethral Suppository
Aminopromazine Fumarate	Aminopromazine Fumarate and Neomycin Sulfate Tablets	
Aminopromazine Fumarate Tablets	Aminopterin Sodium	Aminopromazine Fumarate Injection
Amlodipine	Amlodipine and Benazepril Hydrochloride Capsules	Aminopterin Sodium Tablets
Amphotericin B Injection	Anagrelide Hydrochloride ***(Received)***	Anagrelide Hydrochloride Capsules
Arsenic Trioxide	Arsenic Trioxide Injection	Atovaquone and Proguanil Hydrochloride Tablets
Atovaquone Tablets	Auranofin Capsules	Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets
Azelaic Acid	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium
Balsalazide Disodium Capsules	Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension
Bentoquatam	Bentoquatam Topical Suspension	Benzocaine and Cetylpyridinium Chloride Lozenges
Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets	Bepridil Hydrochloride
Bepridil Tablets	Bivalirudin	Bicalutamide
Bicalutamide Tablets	Brompheniramine Maleate, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride Oral Solution	Bivalirudin Injection
Budesonide ***(Received)***	Budesonide Metered-Dose Inhalation Aerosol	Budesonide Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochloride Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules
Butalbital and Acetaminophen Tablets	Butorphanol Tartrate Nasal Solution ***(Received)***	Cabergoline
Cabergoline Tablets	Calcipotriene	Calcipotriene Cream
Calcipotriene Ointment	Calcipotriene Topical Solution	Calcitriol Capsules
Calcitriol Oral Solution	Calcium Acetate Capsules	Calcium Trisodium Pentetate
Calcium Trisodium Pentetate Injection	Calfactant	Calfactant Intratracheal Suspension
Candesartan Cilexetil	Carbidopa and Levodopa Extended-Release Tablets	Carbidopa and Levodopa Tablets for Oral Suspension
Carbidopa, Levidopa, and Entacapone Tablets	Carmustine ***(Received)***	Carmustine Implant
Carmustine for Injection	Cefdinir	Carvedilol
Carvedilol Tablets	Cefditoren Pivoxil Tablets	Cefdinir Tablets
Cefditoren Pivoxil	Ceftibuten for Oral Suspension	Ceftibuten
Ceftibuten Capsules	Cetirizine Hydrochloride Oral Solution	Ceftiofur Hydrochloride Oral Suspension
Cetirizine Hydrochloride	Cetrorelix Injection	Cetirizine Hydrochloride Tablets

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products) *(Continued)*

Cetrorelix	Chloroxine	Cevimeline
Cevimeline Hydrochloride Capsules	Choline and Magnesium Salicylates Oral Solution	Chloroxine Cream
Chlorpromazine Hydrochloride Extended-Release Capsules	Ciclopirox Shampoo	Choline and Magnesium Salicylates Tablets
Choline Salicylate Oral Solution	Cilostazol ***(Received)***	Ciclopirox Topical Gel
Ciclopirox Topical Solution	Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Cilostazol Tablets
Cimetidine Oral Solution	Citalopram Hydrobromide Oral Solution	Ciprofloxacin Otic Solution
Citalopram Hydrobromide ***(Received)***	Citalopram Hydrobromide Tablets ***(Received)***	Cladribine Injection
Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Clonazepam Orally-Disintegrating Tablets	Clemastine Fumarate Syrup
Clobetasol Propionate Gel	Clotrimazole and Betamethasone Dipropionate Lotion	Clorazepate Dipotassium Capsules
Clorazepate Dipotassium Extended-Release Tablets	Colfosceril and Tyloxapol Suspension	Colestipol Hydrochloride Tablets
Colfosceril	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Compound Undecylenic Acid Cream
Compound Undecylenic Acid Topical Powder	Cyclosporine Modified Oral Solution	Cromolyn Sodium Metered-Dose Nasal Solution
Cyclosporine Modified Capsules	Cysteamine Bitartrate Capsules	Cyclosporine Ointment
Cyclosporine Topical Solution	Dalfopristin	Cytarabine Liposome
Cytarabine Liposome Injection	Dantrolene Sodium Capsules	Dalfopristin and Quinupristin Injection
Dantrolene Sodium	Dapiprazole for Ophthalmic Solution	Dantrolene Sodium for Injection
Dantrolene Sodium Oral Suspension	Desirudin for Injection	Dapirazole Hydrochloride
Desirudin	Dexrazoxane	Desonide ***(Received)***
Desonide Cream	Didanosine ***(Received)***	Didanosine for Oral Solution ***(Received)***
Didanosine Chewable Tablets ***(Received)***	Dextromethorphan Polistirex Extended-Release Oral Suspension	Dexrazoxane for Injection
Dextroamphetamine Sulfate Extended-Release Capsules	Diazepam Injectable Emulsion	Diethylpropion Hydrochloride Extended-Release Tablets
Diclofenac Sodium Ophthalmic Solution	Difloxacin Hydrochloride	Difloxacin Hydrochloride Tablets
Difenoxin and Atropine Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Diltiazem Malate Extended-Release Tablets	Divalproex Sodium Delayed-Release Capsules	Docosanol
Divalproex Sodium ***(Received)***	Dorzolamide Ophthalmic Solution	Doxacurium Chloride Injection
Dorzolamide and Timolol Ophthalmic Solution	Doxycycline Oral Gel	Econazole Nitrate Cream
Doxepin Hydrochloride Cream	Enalapril Maleate and Diltiazem Maleate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Edrophonium Chloride and Atropine Sulfate Injection	Entacapone	Entacapone Tablets
Enalaprilat Injection	Epoprostenol	Epoprostenol For Injection
Ephedrine Sulfate and Guaifenesin Tablets	Erythromycin Phosphate	Erythromycin Thiocyanate
Epoprostenol Injection	Esmolol Hydrochloride Injection	Esomeprazole Magnesium
Esmolol	Estazolam	Estazolam Tablets
Esomeprazole Magnesium Capsules	Estramustine Phosphate Sodium	Estramustine Phosphate Sodium Capsules
Estradiol Benzoate	Ethanolamine Oleate Injection	Etomidate
Etomidate Injection	Etidronate Disodium Injection Concentrate	Ethanolamine Oleate

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products) *(Continued)*

Etoposide Phosphate	Exemestane	Exemestane Tablets
Fentanyl ***(Received)***	Famotidine Injection	Famotidine Orally Disintegrating Tablets
Ferrous Fumarate and Docusate Sodium Extended-Release Capsules	Fentanyl Lozenges	Fentanyl Transdermal System
Fluconazole Injection	Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets
Flunisolide Nasal Spray	Fluconazole Tablets	Flunisolide Inhalation Aerosol
Fluoromethane F 18	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluticasone Propionate Inhalation Powder	Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium
Fosfomycin Tromethamine	Foscarnet Sodium Injection	Fosfomycin For Oral Solution
Gadobenate Dimeglumine	Gabapentin Oral Solution	Gabapentin Tablets
Galantamine	Gadobenate Dimeglumine Injection	Gadopentetic Acid
Gallium Nitrate Injection	Galantamine Hydrobromide Tablets	Gallium Nitrate
Ganirelix Acetate Injection	Ganciclovir Capsules	Ganirelix
Gentamicin Sulfate Oral Solution	Gatifloxacin Injection	Gatifloxacin Tablets
Glipizide Extended-Release Tablets	Gentamicin Sulfate Soluble Powder	Glimepiride Tablets
Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Glyceryl Aminobenzoate	Granisetron
Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution	Granisetron Tablets	Granisetron Injection
Halobetasol Propionate Ointment	Guanidine Hydrochloride Tablets	Halobetasol Propionate
Haloperidol Lactate Injection	Guanidine Hydrochloride	Halobetasol Propionate Cream
Hydrochlorothiazide Oral Solution Concentrate	Haloperidol Decanoate	Haloperidol Decanoate Injection
Hydrocodone Bitartrate and Acetaminophen Oral Solution	Haloperidol Lactate Oral Concentrate	Hydralazine Hydrochloride and Hydrochlorothiazide Capsules
Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrochlorothiazide Capsules	Hydrocodone Bitartrate and Guaifenesin Oral Solution
Hydrocortisone ***(Received)***	Hydrocodone Bitartrate and Aspirin Tablets	Hydrocodone Polistirex
Hydrocortisone Butyrate Lotion	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	Hydrocortisone Acetate Rectal Foam Aerosol
Hydroquinone Lotion	Hydrocortisone Acetate Dental Paste	Hydromorphone Hydrochloride Oral Solution
Ibuprofen Capsules	Hydroflumethiazide and Reserpine Tablets	Ibandronate Sodium Tablets
Imipramine Pamoate Capsules	Ibandronate Sodium	Imipramine Pamoate
Irinotecan	Idarubicin Hydrochloride Injection	Ipratropium Bromide Inhalation Solution
Isosulfan Blue Injection	Ipratropium Bromide Inhalation Aerosol	Isosulfan Blue
Itraconazole Injection	Irinotecan Hydrochloride Injection	Itraconazole
Ketoconazole Shampoo	Isradipine Extended-Release Tablets	Ketoconazole Cream
Ketoprofen Tablets	Itraconazole Oral Solution	Ketoprofen Extended-Release Capsules
Lactic Acid Lotion	Ketoprofen Capsules	Ketotifen Fumarate Ophthalmic Solution
Lamotrigine	Ketotifen Fumarate	Lamotrigine
Lawsone	Lamivudine Tablets	Latanoprost Ophthalmic Solution
Levetriacepam	Latanoprost	Leucovorin Calcium for Injection
Levobetaxolol Ophthalmic Suspension	Lawsone With Dihydroxyacetone	Levobetaxolol
Levofloxacin	Levetriacepam Tablets	Levocabastine Ophthalmic Suspension
Levomethadyl Acetate Hydrochloride Oral Concentrate	Levocabastine Hydrochloride	Levomethadyl Acetate
Liothyronine Injection	Levofloxacin Solution	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products) *(Continued)*

Lomustine Capsules	Lidocaine and Prilocaine Cream ***(Received)***	Lomustine
Lopinavir and Ritonavir Solution	Lisinopril and Hydrochlorothiazide Tablets	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***
Loratadine Orally Disintegrating Tablets	Lopinavir	Lopinavir Solution
Losartan Potassium Tablets	Mesalamine Suppositories	Methacholine Chloride for Inhalation Solution
Mesoridazine Besylate Concentrate	Mefloquine Hydrochloride Tablets	Methoxsalen Softgels
Methadone Hydrochloride Oral Concentrate	Melphalan for Injection	Metipranolol Hydrochloride
Methyclothiazide and Deserpidine Tablets	Metaraminol Bitartrate Injection	Metronidazole Cream
Metipranolol Ophthalmic Solution	Methocarbamol and Aspirin Tablets	Metronidazole Lotion
Metronidazole Extended-Release Tablets	Methylphenidate Hydochloride Chewable Tablets	Midazolam Hydrochloride
Midazolam Hydrochloride Injection	Metronidazole Capsules	Mifepristone
Molindone Hydrochloride Oral Solution	Moexipril	Metronidazole Hydrochloride for Injection
Miconazole Nitrate Topical Aerosol	Misoprostol ***(Received)***	Misoprostol Dispersion ***(Received)***
Misoprostol Tablets ***(Received)***	Milrinone Injection	Mifepristone Tablets
Morphine Sulfate for Injection Concentrate	Mivacurium	Mivacurium in Dextrose Injection
Morphine Sulfate Tablets	Moexipril Hydrochloride and Hydrochlorothiazide Tablets	Morphine Sulfate Oral Solution Concentrate
Mycophenolate Mofetil Tablets	Mivacurium Injection	Mycophenolate Mofetil Oral Solution
Nalmefene Hydrochloride	Moexipril Hydrochloride Tablets	Nalbuphine Hydrochloride Injection
Naproxen Extended-Release Tablets	Morphine Sulfate Oral Solution	Naphazoline Hydrochloride and Phenirамine Maleate Ophthalmic Solution
Neomycin Sulfate Oral Powder	Mycophenolate Mofetil Capsules	Nedocromil Sodium Inhalation Aerosol
Nicardipine Hydrochloride	Nalbuphine Hydrochloride	Nevirapine Tablets
Nilutamide Tablets	Nalmefene Hydrochloride Injection	Nilutamide
Nisoldipine Extended-Release Tablets	Nedocromil	Nisoldipine
Ofloxacin In Dextrose Injection	Nevirapine Oral Suspension	Nizatidine Tablets
Olopatadine	Nicardipine Hydrochloride Capsules	Ofloxacin Tablets
Olsalazine Sodium Capsules	Nimodipine Capsules	Olsalazine Sodium
Orphenadrine Citrate Extended-Release Tablets	Nitroglycerin Solution in Acrylic Adhesive	Ondansetron Tablets
Oxcarbazepine Suspension	Ofloxacin Injection	Orbifloxacin Tablets
Pantoprazole Sodium	Olopatadine Ophthalmic Solution	Oxcarbazepine ***(Received)***
Paroxetine Hydrochloride Extended-Release Tablets	Ondansetron Oral Solution	Oxiconazole Cream
Pemoline	Orbifloxacin	Pancuronium Bromide Injection ***(Received)***
Pentaerythritol Tetranitrate Extended-Release Capsules	Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Pantoprazole Sodium Tablets
Pentamidine Isethionate for Inhalation	Oxcarbazepine Tablets	Pemirolast Potassium Ophthalmic Solution
Permethrin Cream	Pancuronium Bromide ***(Received)***	Penicillin G Potassium Tablets for Oral Solution
Phentermine Resin Complex	Pantoprazole Sodium for Injection	Pentamidine Isethionate
Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Tablets	Paroxetine Oral Suspension	Pentazocine Hydrochloride and Acetaminophen Tablets
Phendimetrazine Tartrate Extended-Release Capsules	Pemoline Tablets	Phenobarbital Capsules

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products) *(Continued)*

Pilocarpine Hydrochloride Ophthalmic Ointment	Pentaerythritol Tetranitrate Extended-Release Tablets	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules
Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pentamidine Isethionate for Injection	Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tabs
Poractant Alpha	Phentermine Resin Complex Capsules	Pilocarpine Hydrochloride Ophthalmic Gel
Povacrylate Solution	Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide
Povidone-Iodine Swabsticks	Pirbuterol Acetate	Pirbuterol Acetate Inhalation Aerosol
Pramipexole Dihydrochloride Tablets	Poractant Alpha Supension	Porfimer Sodium for Injection
Prednicarbate Cream	Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze
Prochlorperazine Maleate Extended-Release Capsules	Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories
Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Prazosin Hydrochloride and Polythiazide Capsules	Prednicarbate ***(Received)***
Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Prednicarbate Ointment	Prednisolone Sodium Phosphate Oral Solution
Pseudoephedrine Hydrochloride And Naproxen Sodium Extended-Release Tablets	Progesterone Capsules	Proguanil
Pseudoephedrine Sulfate And Dexbrompheniramine Maleate Extended-Release Tablets	Promethazine and Phenylephrine Hydrochlorides Syrup	Promethazine Hydrochloride and Codeine Phosphate Oral Solution
Pyrilamine Maleate Injection	Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets
Ranitidine Capsules	Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution
Reserpine and Polythiazide Tablets	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Table
Risperidone Orally Disintegrating Tablets	Quinidine Sulfate Injection	Quetiapine Fumarate
Rivastigmine Tartrate Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets	Ramipril Capsules
Rimantadine Hydrochloride Oral Solution	Risperidone ***(Received)***	Risperidone Tablets
Rosiglitazone Maleate Tablets	Rose Bengal	Risperidone Oral Solution
Salicylic Acid and Sulfur Lotion	Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection
Salmeterol Xinafoate	Rose Bengal Ophthalmic Solution	Ropinirole Hydrochloride Tablets
Scopolamine Transdermal System	Salicylic Acid Cream	Salicylic Acid and Sulfur Cleansing Lotion
Serpacwa Topical Cream	Salicylic Acid and Sulfur Shampoo	Salicylic Acid Ointment
Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder
Sodium Chlorophyllin Copper Complex Tablets	Selegiline Hydrochloride Capsules	Sibutramine Hydrochloride Capsules
Sodium Phenylbutyrate Oral Powder	Sertraline Hydrochloride Oral Solution	Simethicone ***(Received)***
Sodium Phosphates Tablets	Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Phenylbutyrate
Sterile Talc Aerosol	Sodium Iodide Injection	Sodium Phosphates for Oral Suspension
Sucralfate Oral Suspension	Sodium Phenylbutyrate Tablets	Sterile Methotrexate Sodium
Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sodium Salicylate and Sulfur Shampoo	Streptozocin for Injection
Sulisobenzone Lotion	Streptozocin	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension
Tacrolimus	Sulconazole Nitrate Cream	Sulfacytine Tablets

MONOGRAPH NAME
Noncomplex Actives (Drug Substances and Products) *(Continued)*

Tacrolimus Ointment	Sulfacytine	Sulfasalazine Oral Suspension
Tenofovir Disoproxil Fumarate Tablets	Sulfanilamide Vaginal Cream	Sumatriptan Tablets
Terbinafine Tablets	Sumatriptan Injection	Tacrolimus Injection
Terconazole Vaginal Cream	Tacrolimus Capsules	Technetium Tc 99m Teboroxime Injection
Tetracycline Hydrochloride Periodontal Fiber	Tamsulosin Hydrochloride Capsules	Terbinafine Hydrochloride Cream
Tioconazole Vaginal Ointment	Terbinafine Hydrochloride	Terconazole
Tolnaftate Topical Aerosol Solution	Terbinafine Topical Solution	Testosterone Transdermal System
Torsemide Injection	Terconazole Vaginal Suppositories	Tiludronate Disodium
Trandolapril Tablets	Theophylline Extended-Release Tablets	Tiopronin Tablets
Tranylcypromine Sulfate	Tiopronin	Topiramate Tablets
Tretinoin Microsphere Gel	Topiramate Capsules	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets
Trimetrexate for Injection	Torsemide Tablets	Tranexamic Acid Injection
Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Tranexamic Acid	Tretinoin Capsules
Trolamine Salicylate Topical Emulsion	Tranylcypromine Sulfate Tablets	Trifluridine Ophthalmic Solution
Trovafloxacin Mesylate for Injection	Triamcinolone Acetonide Metered-Dose Nasal Suspension	Trimipramine Maleate Capsules
Urea Cream	Trimipramine Maleate	Trolamine Salicylate Gel
Valproic Acid Injection ***(Received)***	Trolamine Salicylate Cream	Trovafloxacin Mesylate
Venlafaxine Tablets	Trovafloxacin Injection	Unoprostone Isopropyl Ophthalmic Solution
Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Undecylenic Acid Topical Foam Aerosol
Venlafaxine Extended-Release Capsules	Vecuronium Bromide for Injection	Yttrium Y-90 Glass Microspheres
Yttrium Y-90 Chloride Solution	Yttrium Y-90 Microspheres Injection	Zidovudine and Lamivudine Tablets
Zinc Tridosium Pentetate	Zinc Tridosium Pentetate Injection	Zinc Acetate Capsules
Ziprasidone Hydrochloride Capsules	Zoledronic Acid for Injection	
Excipients		
Aluminum Stearate	Butylene Glycol	Calcium Alginate
Calcium Glycerophosphate	Calcium Propionate	Calcium Sorbate
Canola Oil	Coconut Oil	Cystine
Dehydroacetic Acid	Desoxycholic Acid	Diethyl Sebacate
Diisopropanolamine ***(Received)***	Erythritol ***(Received)***	Erythorbic Acid
Ethyl Hexanediol	Ethyl Maltol	Gamma-Cyclodextrin
Glycerol Ester Of Gum Rosin (Ester Gum)	Hexanetriol(-1,2,6-)	Lanolin (Wool Fat), Hydrogenated
Lanolin Hydrous	Lauramine Oxide	Linoleic Acid
Macrogol Sorbitan Tristearate	Maltitol ***(Received)***	Microcrystalline Cellulose, Silicified
N-Methylpyrrolidone ***(Received)***	Oleyl Oleate	Palm Kernel Oil
Polyacrylate Dispersion 30 Percent ***(Received)***	Polydextrose	Polyvinyl Acetate
Potassium Alginate ***(Received)***	Potassium Glycerophospate	Propylene Glycol Monolaurate ***(Received)***
Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil	Rapeseed Oil, Hydrogenated
Rapeseed Oil, Superglycerinated	Rosin	Sodium Acid Pyrophosphate
Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic	Sodium Aluminum Phosphate Basic
Sodium Bisulfite	Sodium Citrate, Monobasic	Sodium Diacetate
Sodium Erythorbate	Sodium Polyphosphates Glassy	Sodium Pyrophosphate
Sodium Sesquicarbonate	Sodium Thiomalate	Sodium Trimetaphosphate
Sodium Tripolyphosphate	Soy Polysaccharides	Stannous Chloride
Stearyl Citrate	Succinylated Monoglycerides	Sucrose Stearate
Sulfobutyl Ether Beta Cyclodextran	Tallow Glycerides	Wheat Gluten

USP ANNUAL SCIENTIFIC MEETING, SEPTEMBER 27–30, 2005: IMPACT THE FUTURE OF PHARMACOPEIAL STANDARDS. The USP Annual Scientific Meeting will be held in the Hotel del Coronado, Coronado, California, September 27–30, 2005.

Spread the word. Tell your colleagues and register at: www.usp.org/conferences, 301-816-8134.

The USP 2005 Annual Scientific Meeting is your opportunity to directly contribute to USP's standards-setting processes. Through interaction with USP's scientific staff and Council of Experts, you will help establish standards-setting priorities for the organization and help shape the quality requirements that you must, by law, follow.

Featuring:

Analytical Validation and Verification of Compendial Methods

Learn about the new USP information in General Informational Chapter ⟨1226⟩ *Verification of Compendial Procedures.* Also includes presentations and workshops on the requirements for evolving analytical validation procedures, including spectroscopic and other physical test methods.

Biologics and Biotechnology Derived Therapies

Interactive discussion on cross-cutting, standards-setting activities currently being undertaken by USP, including validation of bioassays, development of standards for ancillary materials and international activities in biological standardization.

Dietary Supplements

Learn about the current and future impact of dietary supplement verification and new FDA regulatory initiatives on the marketplace; expansion of General Information Chapter ⟨2030⟩ *Supplemental Information for Botanicals;* technologies for botanical classification, and identification and analysis of new/emerging/potential dietary supplement ingredients.

Excipients

Interact with USP scientific experts, FDA, industry, and academic experts to discuss the science and related issues of excipients quality, including additives, excipient functionality and its impact on formulation, and multisource excipient equivalence, as well as recent advances in the development of novel excipients.

Making *USP–NF* Work for You

Be among the first to learn about future directions and updates based on resolutions adopted at the 2005 USP Convention and through other USP initiatives.

Annual Scientific Meeting 2005 Exhibit Program

Network with your colleagues as they showcase what's new and upcoming in the industry.

WHO SHOULD ATTEND:

- *USP-NF* and USP Reference Standards Users
- Scientists focusing on chemistry, biologics and biotechnology, analytical validation, excipients, and dietary supplements
- Government representatives
- Academia and association representatives
- Regulatory Affairs personnel
- R&D and QC personnel
- Lab supervisors/managers
- Compendial Affairs personnel
- Statisticians
- Technical consultants
- Healthcare practitioners

New and experienced bench chemists who want to better understand the USP process also may wish to attend the "Making *USP–NF* Work for You" track.

SCHEDULE:

Day 1—	September 27, 2005:	Registration
Day 2—	September 28, 2005:	The Annual Scientific Meeting starts with an opening session in the morning followed by Track Session I in the afternoon
Day 3—	September 29, 2005:	Track Session II (morning) and Track Session III (afternoon)
Day 4—	September 30, 2005:	Track Session IV in the morning followed by a "Town Hall" discussion. Meeting adjourns at 12:30 p.m.

Extension Services in Pharmacy at the University of Wisconsin-Madison School of Pharmacy is accredited by the Accreditation Council on Pharmacy Education (ACPE, formerly the American Council on Pharmaceutical Education) as a provider of continuing pharmaceutical education. This program is approved for 14.5 hours or 1.45 continuing education units (CEUs).

In order to receive credit, pharmacists will be required to complete an Annual Scientific Meeting evaluation form. In addition, pharmacists must complete a statements of credit form for continuing pharmaceutical education participation which will be mailed (by USP) within one month after the meeting. ACPE number: 073-999-05-076-L04 through 073-999-05-081-L04.

ADVANCE NOTICE OF UPCOMING OFFICIAL REVISIONS TO THE *USP–NF.* In order to provide as much time as possible for industry to adopt revisions made to the compendia, upcoming official revisions to the *USP–NF* are now being announced on the USP website as soon as they are voted on to become official by the appropriate Expert Committees of the Council of Experts.

Readers are directed to the ''Notices'' section found in the top right corner of the USP homepage at www.usp.org. By clicking on ''Upcoming Official Revisions to the *USP–NF:* Reference Standards Required But Not Available,'' you are taken to a page where upcoming revisions to the compendia are listed. The information posted includes the title of the item being revised, the *PF* citation where the revision was proposed, and a description of the proposal. In addition, an e-mail link to the USP Scientific Liaison for each revision is listed in parentheses after the item. The actual content and official date of each revision will be published in either an annual edition, *Supplement,* or *Interim Revision Announcement* and the items are sorted according to the publication in which they are to appear.

In addition, readers will also find a list of new USP Reference Standards that correspond to new *USP–NF* monographs but unfortunately are not yet available. The official dates of any *USP–NF* Standards, tests, or assays that require the use of these Standards are postponed until further notice pending availability of the Standards.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE *USP–NF.* The *USP Guideline for Submitting Requests for Revision to the USP–NF* is available on USP's website at www.usp.org. 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 Noncomplex 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 courses offer specialized instruction for chemists, scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2005 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

2005 Calendar of Pharmacopeial Education Courses

Date	Name of Course	Location
July 18 and 19	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
August 12	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
August 17	Analytical Method Validation	USP Headquarters, Rockville, MD
August 18	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
August 19	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
October 19 and 20	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 7	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 8	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	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 PRINT, ONLINE, AND CD.** *USP–NF,* the authoritative reference for official pharmaceutical standards is available in three convenient formats—print, online, and CD. One main edition and two *Supplements* are published each year. The current edition, *USP 28–NF 23*, is official through 2005. Starting with the *Second Supplement* to *USP 28–NF 23,* which will be available in June 2005, the *USP–NF* Online and CD versions will feature several enhancements. The enhancements include ''My *USP–NF,*'' an exciting new option that lets subscribers customize their use of *USP–NF* by saving frequent searches, creating a unique table of contents, and using other personalization options. To order *USP–NF,* go to www.usp.org or call 1-800-227-8772 or 301-881-0666.

CHROMATOGRAPHIC REAGENTS. Official and proposed chromatographic procedures in the *USP–NF* and *Pharmacopeial Forum (PF)* refer to column reagents only by 'L,' 'S,' or 'G' designations. The brand names of these reagents are listed in *Chromatographic Reagents.* This book also provides an index of column manufacturers and lists alternative columns that may be used to carry out official procedures. *Chromatographic Reagents* saves chemists and scientists valuable laboratory time spent searching for the right columns to use in testing. *Chromatographic Reagents* is available in print format. The online format of the *USP–NF* includes the latest *Chromatographic Reagents*. To order *Chromatographic Reagents,* go to www.usp.org or call 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
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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.

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.

Publication and Comment Schedule for *USP 29–NF 24*

Publication	Comment Deadline	Publication Date	Official Date
Main Book	May 15, 2005	November 2005	January 2006
Supplement One	August 15, 2005	February 2006	April 2006
Supplement Two	December 16, 2005	June 2006	August 2006

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. 2005	Apr. 1, 2005
PF 31(2) [Mar.–Apr. 2005]	Mar. 2005	Not Applicable
2nd IRA [published in *PF* 31(2)]	Mar. 2005	Apr. 1, 2005
PF 31(3) [May–June 2005]	May 2005	Not Applicable
3rd IRA [published in *PF* 31(3)]	May 2005	June 1, 2005
2nd Supplement	June 2005	Aug. 1, 2005
PF 31(4) [July–Aug. 2005]	July 2005	Not Applicable
4th IRA [published in *PF* 31(4)]	July 2005	Aug. 1, 2005
PF 31(5) [Sept.–Oct. 2005]	Sept. 2005*	Not Applicable
5th IRA [published in *PF* 31(5)]	Sept. 2005*	Oct. 1, 2005*
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005*	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005*	Dec. 1, 2005*
PF 32(1) [Jan.–Feb. 2006]	Jan. 2006*	Not Applicable
1st IRA [published in *PF* 32(1)]	Jan. 2006*	Feb. 1, 2006*
1st Supplement	Feb. 2006*	Apr. 1, 2006*
PF 32(2) [Mar.–Apr. 2006]	Mar. 2006*	Not Applicable
2nd IRA [published in *PF* 32(2)]	Mar. 2006*	Apr. 1, 2006*
PF 32(3) [May–June 2006]	May 2006*	Not Applicable
3rd IRA [published in *PF* 32(3)]	May 2006*	June 1, 2006*
2nd Supplement	June 2006*	Aug. 1, 2006*
PF 32(4) [July–Aug. 2006]	July 2006*	Not Applicable
4th IRA [published in *PF* 32(4)]	July 2006*	Aug. 1, 2006*
PF 32(5) [Sept.–Oct. 2006]	Sept. 2006*	Not Applicable
5th IRA [published in *PF* 32(5)]	Sept. 2006*	Oct. 1, 2006*
PF 32(6) [Nov.–Dec. 2006]	Nov. 2006*	Not Applicable
6th IRA [published in *PF* 32(6)]	Nov. 2006*	Dec. 1, 2006*

* 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 (*USP27*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 27*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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.

FOURTH INTERIM REVISION ANNOUNCEMENT to *USP 28* and to *NF 23*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Eric B. Sheinin, Ph.D., *Chief Science Officer*

Official August 1, 2005 **Released July 1, 2005**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of *USF–NF* users.

USP Ademetione Disulfate Tosylate RS (January 1, 2006)
USP Adipic Acid RS (September 1, 2005)
USP Agnuside RS (November 1, 2005)
USP Aluminum Sulfate (AS)
USP Amiodarone Hydrochloride RS (July 1, 2005)
USP Ammonium Phosphate Dibasic (AS)
USP Ascorbyl Palmitate RS (September 1, 2005)
USP Asparagine Anhydrous RS (November 1, 2005)
USP Asparagine Monohydrate RS (November 1, 2005)
USP Bismuth Subcarbonate RS (September 1, 2005)
USP Bismuth Subgallate RS (September 1, 2005)
USP Bismuth Subnitrate RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound A RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound B RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound C RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound F RS (January 1, 2006)
USP Calcium Stearate (AS)
USP Carboxymethylcellulose Calcium (AS)
USP Carboxymethylcellulose Sodium RS (September 1, 2005)
USP Carprofen RS (September 1, 2005)
USP Casticin RS (November 1, 2005)
USP Microcrystalline Cellulose (AS)
USP Powdered Cellulose (AS)
USP Ciclopirox RS (January 1, 2006)
USP Ciclopirox Related Compound A RS (January 1, 2006)
USP Ciclopirox Related Compound B RS (January 1, 2006)
USP Cromolyn Sodium Related Compound A (AS)
USP 2-Deoxy-D-glucose RS (November 1, 2005)
USP Desoaminylazithromycin RS (January 1, 2006)
USP Dextran 1 RS (July 1, 2005)
USP Dextran T-10 RS (July 1, 2005)
USP Dibutyl Sebacate (AS)
USP Dichlorvos (AS)
USP Diethanolamine RS (November 1, 2005)
USP Eleutheroside B RS (January 1, 2006)
USP Eleutheroside E RS (January 1, 2006)
USP Enrofloxacin RS (January 1, 2006)
USP Eugenol RS (November 1, 2005)
USP Fexofenadine Hydrochloride RS (July 1, 2005)
USP Fexofenadine Related Compound A RS (July 1, 2005)
USP Fexofenadine Related Compound B RS (July 1, 2005)
USP Fluconazole RS (July 1, 2005)
USP Fluconazole Related Compound A RS (July 1, 2005)
USP Fluconazole Related Compound B RS (July 1, 2005)
USP Fluconazole Related Compound C RS (July 1, 2005)
USP Fludeoxyglucose Related Compound A RS (September 1, 2005)
USP Fluvoxamine Maleate RS (November 1, 2005)
USP L-Fucose RS (November 1, 2005)
USP Galactitol RS (January 1, 2006)
USP Hypromellose Acetate Succinate RS (July 1, 2005)
USP Indapamide Related Compound A (AS)
USP Indinavir RS (September 1, 2005)
USP Indinavir System Suitability RS (September 1, 2005)
USP Isopropyl Alcohol RS (September 1, 2005)
USP Lactic Acid (AS)
USP Lauroyl Polyoxylglycerides (AS)
USP Losartan Potassium RS (July 1, 2005)
USP Lutein RS (September 1, 2005)
USP Magnesium Carbonate (AS)
USP Magnesium Stearate (AS)
USP Maltose Monohydrate RS (January 1, 2006)
USP Mangafodipir Related Compound A RS (July 1, 2005)
USP Mangafodipir Related Compound B RS (July 1, 2005)
USP Mangafodipir Trisodium RS (July 1, 2005)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Meglumine RS (September 1, 2005)
USP Melengestrol Acetate RS (September 1, 2005)
USP Melengestrol Acetate Related Compound A RS (September 1, 2005)
USP Melengestrol Acetate Related Compound B RS (September 1, 2005)
USP Metacholine Chloride (AS)
USP Methyl Salicylate RS (September 1, 2005)
USP Monobasic Potassium Phosphate (AS)
USP Monoethanolamine RS (November 1, 2005)
USP Monosodium Glutamate RS (September 1, 2005)
USP Morantel Tartrate RS (September 1, 2005)
USP Oleic Acid RS (November 1, 2005)
USP Olive Oil (AS)
USP Omeprazole Related Compound A RS (September 1, 2005)
USP Pancuronium Bromide RS (September 1, 2005)
USP Peanut Oil (AS)
USP Phenoxyethanol RS (July 1, 2005)
USP Phenylethyl Alcohol RS (November 1, 2005)
USP Phosphoric Acid (AS)
USP Potassium Acetate (AS)
USP Potassium Bitartrate (AS)
USP Potassium Citrate RS (September 1, 2005)
USP Potassium Nitrate (AS)
USP Dibasic Potassium Phosphate (AS)
USP Potassium Sodium Tartrate RS (September 1, 2005)
USP Potassium Sorbate (AS)
USP Prilocaine RS (January 1, 2006)
USP Prilocaine Related Compound A RS (January 1, 2006)
USP Propofol RS (January 1, 2006)
USP Propofol Related Compound A RS (January 1, 2006)
USP Propofol Related Compound B RS (January 1, 2006)
USP Propofol Related Compound C RS (January 1, 2006)
USP Propofol Resolution Mixture C RS (January 1, 2006)
USP Ramipril Related Compound D RS (November 1, 2005)
USP Residual Solvent Class 2—Hexane RS (November 1, 2005)
USP Residual Solvents Class 2—Mixture B RS (January 1, 2006)
USP Sevoflurane Related Compound B RS (July 1, 2005)
USP Sevoflurane Related Compound C RS (July 1, 2005)
USP β-Sitosterol RS (September 1, 2005)
USP Sodium Bicarbonate (AS)
USP Sodium Benzoate RS (January 1, 2006)
USP Sodium Chloride (AS)
USP Sorbic Acid (AS)
USP Stavudine RS (January 1, 2006)
USP Stavudine System Suitability Mixture RS (January 1, 2006)
USP Sulfaquinoxaline Related Compound A RS (January 1, 2006)
USP Sumatriptan Succinate Related Impurities RS (November 1, 2005)
USP Tagatose RS (January 1, 2006)
USP Tannic Acid RS (September 1, 2005)
USP Tartaric Acid RS (September 1, 2005)
USP Terbutaline Related Compound A RS (September 1, 2005)
USP Thymol RS (November 1, 2005)
USP Tilmicosin RS (November 1, 2005)

USP Tolcapone RS (July 1, 2005)
USP Tolcapone Related Compound B RS (September 1, 2005)
USP Trenbolone CIII RS (November 1, 2005)
USP Trenbolone Acetate CIII RS (November 1, 2005)
USP Tribasic Calcium Phosphate (AS)
USP Trolamine RS (November 1, 2005)
USP Tylosin Tartrate RS (September 1, 2005)
USP Urea RS (September 1, 2005)

The official dates of any *USP 28* or *NF 23* 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 Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Berberine Chloride RS
USP Budesonide RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Cetrimonium Bromide RS
USP Clopidogrel Bisulfate RS
USP Clopidogrel Bisulfate Related Compound A RS
USP Clopidogrel Bisulfate Related Compound B RS
USP Clopidogrel Bisulfate Related Compound C RS
USP Copolymer Polypropylene RS
USP Cytosine RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluticasone Propionate Resolution Mixture RS
USP Fluticasone Propionate System Suitability Mixture RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Hydrastine Hydrochloride RS
USP Insulin Lispro RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Mecamylamine Related Compound A RS
USP Mefloquine Hydrochloride RS
USP Mefloquine Related Compound A RS
USP Menotropins RS
USP Methyldopa-glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Related Compound A RS
USP Naratriptan Related Compound B RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Norphenylephrine Hydrochloride RS
USP Ondansetron RS
USP Paricalcitol Solution RS
USP Maritime Pine Extract RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Polyoxyl 20 Cetostearyl Ether RS
USP Polyoxyl 20 Stearyl Ether RS
USP Posterior Pituitary RS
USP Potassium Perchlorate RS
USP Proinsulin (Beef) RS
USP Proinsulin (Pork) RS
USP Propofol for System Suitability RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Ropivacaine Hydrochloride RS
USP Ropivacaine Related Compound A RS
USP Ropivacaine Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tiagabine Related Compound A RS
USP Racemic Tiagabine Hydrochloride Mixture RS
USP Tiagabine Hydrochloride RS
USP Tinidazole Related Compound B RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS

NOTICE OF POSTPONEMENT

Helium, Nitrous Oxide, Nitrogen, and *Nitrogen 97 Percent*

USP has **postponed indefinitely** the official dates of the revisions to the *Helium, Nitrous Oxide, Nitrogen,* and *Nitrogen 97 Percent* monographs, which were published in the *First Supplement* to *USP 28–NF 23* on pages 3245, 3264, 3359, and 3359, respectively. These revisions were originally slated to become official on April 1, 2005. The postponements are intended to provide additional time to further evaluate some of the tests, procedures, and acceptance criteria provided in the proposed revisions.

The Aerosols Expert Committee is presently reviewing comments received concerning these revisions. The USP intends to publish, if necessary, additional proposed revisions in a future issue of *Pharmacopeial Forum* for further public review and comment. USP proposes that these monograph revisions go forward to official text once the public comments have been considered.

Should you have any questions, please contact Kahkashan Zaidi, Ph.D., Scientist, General Policies and Requirements Division and liaison to the Aerosols Expert Committee (301-816-8269 or kxz@usp.org).

Helium

Change to read:

•**USP Reference standards** ⟨11⟩—*USP Air–Helium RS.*•

•(Postponed indefinitely)•

Change to read:

Assay—Introduce a specimen of Helium into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of nitrogen and oxygen from Helium, although the nitrogen and oxygen may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •USP Air–Helium RS,• and indicates not more than 1.0% of air when compared to the peak response of the •USP Air–Helium RS,• and not less than 99.0%, by volume, of He.

•(Postponed indefinitely)•

Nitrous Oxide

Change to read:

•**USP Reference standards** ⟨11⟩—*USP Air–Helium RS. USP Nitrous Oxide RS.*•

•(Postponed indefinitely)•

Change to read:

Identification—

A: With the container temperatures the same and maintained between 15° and 25°, concomitantly read the pressure of the Nitrous Oxide container and of a container of •USP Nitrous Oxide RS.• [NOTE—Do not use the •USP Nitrous Oxide RS• if it has been depleted to less than half of its full capacity.] The pressure of the Nitrous Oxide container is within 50 psi of that of the •USP Nitrous Oxide RS.•

B: Pass 100 ± 5 mL released from the vapor phase of the contents of the Nitrous Oxide container through a carbon dioxide detector tube at the rate specified for the tube: no color change is observed *(distinction from carbon dioxide).*

C: Collect about 100 mL of the gas under test in a 100-mL tube fitted at the top with a stopcock. Open the stopcock, and quickly add a freshly prepared solution of 500 mg of pyrogallol in 2 mL of water and a freshly prepared solution of 12 g of potassium hydroxide in 8 mL of water. Immediately close the stopcock, and mix: the gas is not absorbed, and the solution does not become brown *(distinction from oxygen).*

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NOTICE OF POSTPONEMENT (*continued*)

•**D:** Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrous Oxide RS and a sample of Nitrous Oxide into the gas chromatograph. The retention time of the major peak in the chromatogram of the Nitrous Oxide sample corresponds to that in the chromatogram of the USP Nitrous Oxide RS.•4

•(Postponed indefinitely)•4

Change to read:

Assay—Introduce a specimen of Nitrous Oxide taken from the liquid phase, as directed in the test for *Nitrogen dioxide,* into a gas chromatograph by means of a gas-sampling valve. Select the operating conditions of the gas chromatograph such that the peak response resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of N_2 and O_2 from N_2O, although the N_2 and O_2 may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •USP Air–Helium RS,•4 and is equivalent to not more than 1.0% of air when compared to the peak response of the •USP Air–Helium RS,•4 indicating not less than 99.0%, by volume, of N_2O.

•(Postponed indefinitely)•4

Nitrogen

Change to read:

•**USP Reference standards** ⟨11⟩*—USP Nitrogen RS. USP Oxygen–Helium RS.*•4

•(Postponed indefinitely)•4

Change to read:

Identification—•Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrogen RS and the nitrogen sample into the gas chromatograph. The retention time of the major peak in the chromatogram of the nitrogen sample corresponds to that in the chromatogram of the USP Nitrogen RS.•4

•(Postponed indefinitely)•4

Change to read:

Assay—Introduce a specimen of Nitrogen into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 3 m in length and 4 mm in inside diameter and is packed with a molecular sieve prepared from a synthetic alkali-metal aluminosilicate capable of absorbing molecules having diameters of up to 0.5 nm, which permit complete separation of oxygen from nitrogen. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •the USP Oxygen–Helium RS,•4 and is equivalent to not more than 1.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•4 indicating not less than 99.0%, by volume, of N_2.

•(Postponed indefinitely)•4

Nitrogen 97 Percent

Change to read:

•**USP Reference standards** ⟨11⟩*—USP Nitrogen 97 Percent RS. USP Oxygen–Helium RS.*•4

•(Postponed indefinitely)•4

Change to read:

Identification—•Prepare a gas chromatograph as directed in the *Assay,* and inject USP Nitrogen 97 Percent RS and a sample of Nitrogen 97 Percent into the gas chromatograph. The retention time of the major peak in the chromatogram of the test sample corresponds to that in the chromatogram of the USP Nitrogen 97 Percent RS.•4

•(Postponed indefinitely)•4

Change to read:

Assay—Proceed as directed in the *Assay* under *Nitrogen.* The peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •the USP Oxygen–Helium RS•4 and is equivalent to not more than 3.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•4 indicating not less than 97.0%, by volume, of N_2.

•(Postponed indefinitely)•4

MONOGRAPHS (USP)

Anhydrous Citric Acid

Delete the following:

•**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.•4

Citric Acid Monohydrate

Change to read:

Color of solution—

Standard stock solutions—Prepare three solutions, *A, B,* and *C,* containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g per L):

A—2.4 : 0.6 : 0 : 7.0
B—2.4 : 1.0 : 0.4 : 6.2
C—9.6 : 0.2 : 0.2 : 0

•*Standard solutions*—[NOTE—Prepare the *Standard solutions* immediately before use.] Transfer 2.5 mL of *Standard stock solution A* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution A*. Transfer 2.5 mL of *Standard stock solution B* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution B*. Transfer 0.75 mL of *Standard stock solution C* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution C*.•4

Test solution—Use the *Test solution* prepared in the *Clarity of solution* test.

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 A, Standard solution B, Standard solution C,* and water to separate matching test tubes. Compare the *Test solution, Standard solution A, Standard solution B, Standard solution C,* and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* is not more intensely colored than *Standard solutions A, B, C,* or water.

Clarithromycin Extended-Release Tablets

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.•4

Change to read:

•**Dissolution** ⟨711⟩—

TEST 1—•4

Medium: 0.3 M phosphate buffer, pH 6.0 (prepared by dissolving 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mixing, and diluting with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05); 900 mL.

Apparatus 2: 75 rpm.

Times: 30, 45, 60, and 120 minutes.

Procedure—Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

Standard solutions—Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted in *Medium,* with known concentrations over the range of about 60 to 600 µg per mL.

Test solution—Use portions of the solution under test passed through a 35-µm polyethylene filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the five *Standard solutions* and the *Test solution* into the chromatograph, and measure the responses for the major peaks. Perform a linear regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Test solution* and the linear regression statistics for the *Standard solutions.*

Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to the following *Acceptance Table.*

Acceptance Table

Level	Time (minutes)	Amount dissolved (individual limits)	Amount dissolved (average limits)
L_1	30	not more than 65%	—
	45	between 55 and 85%	—
	60	not less than 75%	—
	120	not less than 85%	—
L_2	30	not more than 75%	not more than 65%
	45	between 45% and 95%	between 55% and 85%
	60	not less than 65%	not less than 75%
	120	not less than 75%	not less than 85%
L_3	30	not more than 2 tablets release more than 75%, and no individual tablet releases more than 85%	not more than 65%
	45	not more than 2 tablets are outside the range of 45% to 95%, and no individual tablet is outside the range of 35% to 105%	between 55% and 85%

Acceptance Table *(Continued)*

Level	Time (minutes)	Amount dissolved (individual limits)	Amount dissolved (average limits)
	60	not more than 2 tablets release less than 65%, and no individual tablet releases less than 55%	not less than 75%
	120	not more than 2 tablets release less than 75%, and no individual tablet releases less than 65%	not less than 85%

•TEST 2—

Medium: 0.05 M phosphate buffer, pH 6.8 containing 0.5% of sodium lauryl sulfate; 900 mL, degassed by sonication and vacuum.

Apparatus 1: 100 rpm.

Times: 2, 12, and 24 hours.

Procedure—Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

0.067 M Phosphate buffer, pH 2.5—Dissolve 9.2 g of monobasic sodium phosphate monohydrate in about 800 mL of water. Adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *0.067 M Phosphate buffer, pH 2.5* (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 56 mg of USP Clarithromycin RS, accurately weighed, to a 100-mL volumetric flask. Add 10 mL of methanol and sonicate to dissolve. Dilute with *Medium* to volume.

Test solution—Centrifuge the solution under test at 2500 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-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. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 2000; 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 *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution.*

Calculate the amount, in percentage, of clarithromycin dissolved with volume correction:

$$\frac{\{C_n \times [900 - V_U (n-1)]\} + [\sum_{i=1}^{n-1} C_i \times V_U] \times 100}{LC}$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each timepoint; n is the number of time points [NOTE—The summation of the amount of clarithromycin removed at previous sampling time points is applicable only where $n > 1$)]; 100 is the conversion factor to percentage; and *LC* is the Tablet label claim.

Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 20%
12	between 45% and 70%
24	not less than 80%

•4

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:

USP Bupropion Hydrochloride Related Compound A RS [2-(*tert*-butylamino)-4′-chloropropiophenone hydrochloride] ($C_{13}H_{18}ClNO \cdot HCl$ ✧ 276.21)—Do not dry. •Keep container tightly closed. Protect from light. Store in a freezer.•4

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Change to read:

USP Bupropion Hydrochloride Related Compound C RS [1-(3-chlorophenyl)-2-hydroxy-1-propanone] ($C_9H_9O_2Cl$ ✧ 184.62)—Do not dry. •Protect from light. Store in a freezer. After opening ampul, store in a tightly closed container.•(4)

Change to read:

USP Bupropion Hydrochloride Related Compound F RS [1-(3-chlorophenyl)-1-hydroxy-2-propanone] ($C_9H_9O_2$ ✧ 184.62)—Do not dry. •Protect from light. Store in a freezer. After opening ampul, store in a tightly closed container.•(4)

Change to read:

USP Cefoxitin RS—•This is the monohydrate form. Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed. Protect from light. Store in a freezer.•(4)

Add the following:

•**USP Ciclopirox RS**—Do not dry. Keep container tightly closed. Store in a refrigerator.•(4)

Add the following:

•**USP Ciclopirox Related Compound A RS** [3-cyclohexyl-4,5-dihydro-5-methyl-5-isoxazolyl acetic acid]—Do not dry. Keep container tightly closed. Store in a refrigerator.•(4)

Add the following:

•**USP Ciclopirox Related Compound B RS** [6-cyclohexyl-4-methyl-2-pyrone]—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•(4)

Change to read:

USP Clindamycin Palmitate Hydrochloride RS—•Do not dry. Keep container tightly closed. Store in a freezer.•(4)

Add the following:

•**USP Desoaminylazithromycin RS**—Do not dry. Keep container tightly closed. Store in a refrigerator.•(4)

Change to read:

USP Fludeoxyglucose RS•—Do not dry. Keep container tightly closed. Protect from light.•(4)

Change to read:

USP L-Methionine RS—•Do not dry.•(4) Keep container tightly closed.

Add the following:

•**USP Nitrofurantoin Related Compound A RS** [*N*-(aminocarbonyl)-*N*-[([5-nitro-2-furanyl]methylene)amino]glycine]—Do not dry. Keep container tightly closed. Protect from light.•(4)

Change to read:

USP Phenytoin RS—•Do not dry.•(4) Keep container tightly closed.

Change to read:

USP Propofol RS•—Do not dry. After opening, keep in tight, light-resistant containers under inert gas.•(4)

Change to read:

USP Propofol Related Compound A RS [3,3′-5,5′-tetraisopropyldiphenol]•—Do not dry. Store in a refrigerator. Protect from light.•(4)

Change to read:

USP Propofol Related Compound B RS [2,6-diisopropylbenzoquinone]•—Do not dry. Keep in tight, light-resistant containers under inert gas. Store in a refrigerator.•(4)

Change to read:

■**USP Stavudine RS**■(1S) *(USP28)*•—Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.•(4)

Change to read:

■**USP Stavudine System Suitability Mixture RS**—It is a mixture of stavudine and the following related compounds: thymidine, thymine, alpha-stavudine, and *xylo*-thymidine.■(1S) *(USP28)*•—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•(4)

Change to read:

USP Sulfaquinoxaline Related Compound A RS [N^1-N^2-diquinoxalin-2-ylsulfanilamide] ($C_{22}H_{16}N_6SO_2$ ✧ 428.50)•—Do not dry. Keep container tightly closed. Protect from light.•(4)

Change to read:

USP Tobramycin RS—•Do not dry. Store in a refrigerator. The material is hygroscopic.•(4)

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ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
1174	*Magnesium Salicylate Tablets*	*Dissolution*	Line 11 under *Dissolution:* Change "(298.54/276.24)(900*C*)(A_S/A_S)" to: (298.54/276.24)(900*C*)(A_U/A_S)
1867	*Terazosin Hydrochloride*	*Limit of tetrahydro-2-furancarboxylic acid*	Line 6 under *Procedure:* Change "100(*C*/*W*)(R_U/R_S)," to: (*C*/*W*)(R_U/R_S),
3080	*Sodium Starch Glycolate*	*Identification*	Line 2: Change "iodine and potassium iodide TS" to: iodine and potassium iodide TS1
Supplement 1			
3290	⟨11⟩ *USP Reference Standards*	*USP Fluticasone Propionate System Suitability Mixture RS*	Lines 2 and 3: Change "It is a mixture of USP Fluticasone Propionate RS and fluticasone propionate related compounds A, B, C, D, and E." to: It is a mixture of USP Fluticasone Propionate RS and fluticasone propionate related compounds B, C, and D.

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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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24*; and

■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*, ■2S (*USP 28*) indicates that the proposed revision is slated for the *Second Supplement to USP 28*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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.

MONOGRAPHS (USP)

BRIEFING

Acetaminophen, *USP 28* page 16. On the basis of comments received, it is proposed to modify the storage conditions in the *Packaging and storage* section.

(PA2: C. Anthony) RTS—41271-1

Change to read:

Packaging and storage—Preserve in tight, light-resistant containers and store at ~~controlled~~

■ ■2S (*USP29*)
room temperature.

■Protect from moisture and heat.■2S (*USP29*)

BRIEFING

Medical Air, *USP 28* page 54; **Carbon Dioxide,** *USP 28* page 349; **Cyclopropane,** *USP 28* page 559; **Helium,** *USP 28* page 939, page 3245 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 707 of *PF* 31(3) [May–June 2005]; **Nitrous Oxide,** *USP 28* page 1388, page 3264 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 707 of *PF* 31(3) [May–June 2005]; **Oxygen,** *USP 28* page 1442; **Oxygen 93 Percent,** *USP 28* page 1443; **Nitrogen,** *NF 23* page 3041, page 3359 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 708 of *PF* 31(3) [May–June 2005]; **Nitrogen 97 Percent,** *NF 23* page 3041, page 3359 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 708 of *PF* 31(3) [May–June 2005]. The *Packaging and storage* section in the monograph is revised to address the issues concerning medical gas mixups. The Definition of the monograph is also revised for clarity.

(AER: K. Zaidi) RTS—42651-1

Change to read:

» Medical Air is a natural or synthetic mixture of gases consisting largely of nitrogen and oxygen. It contains not less than 19.5 percent and not more than 23.5 percent, ~~by volume~~

■volume/volume,■2S (*USP29*)
of O_2.

Change to read:

Packaging and storage~~— Preserve in cylinders or in a low-pressure collecting tank.~~

■Preserve in yellow cylinders or in a yellow low-pressure collecting tank. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)
Containers used for Medical Air are not to be treated with any toxic, sleep-inducing, or narcosis-producing compounds, and are not to be treated with any compound that would be irritating to the respiratory tract when the Medical Air is used.

NOTE—Reduce the container pressure by means of a regulator. Measure the gases with a gas volume meter downstream from the detector tube in order to minimize contamination or change of the specimens.The various detector tubes called for in the respective tests are listed under *Reagent Specifications* in the section *Reagents, Indicators, and Solutions.*

In-Process Revision

BRIEFING

Amiloride Hydrochloride and Hydrochlorothiazide Tablets, *USP 28* page 118. It is proposed to include the formulas for the calculation of the amounts released in the test for *Dissolution.*

(BPC: M. Marques) RTS—42507-2

Change to read:

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.

■*Amiloride standard solution*—Transfer about 60 mg of USP Amiloride Hydrochloride RS (equivalent to about 52 mg of anhydrous amiloride hydrochloride), accurately weighed, to a 200-mL volumetric flask. Dissolve in and dilute with methanol to volume. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume.

Hydrochlorothiazide standard solution—Transfer about 100 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with methanol to volume. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume. Transfer 10.0 mL of the resulting solution to a 50-mL volumetric flask, and dilute with *Medium* to volume.

Test solution 1—Pass a portion of the solution under test through a 0.45-µm glass fiber filter.

Test solution 2—Transfer 5.0 mL of *Test solution 1* to a 25-mL volumetric flask, and dilute with *Medium* to volume.■2S *(USP29)*

Procedure—Determine the amounts of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by employing UV absorption at the wavelengths of maximum absorbance at about 363 nm for amiloride hydrochloride and 270 nm for hydrochlorothiazide

■using *Medium* as the blank.■2S *(USP29)* ~~(corrected for interference from amiloride hydrochloride on the basis of the absorbances of amiloride hydrochloride at 270 nm and 363 nm) on filtered portions of the solution under test, suitably diluted with 0.1 N hydrochloric acid, in comparison with Standard solutions having known concentrations of USP Amiloride Hydrochloride RS and USP Hydrochlorothiazide RS in the same *Medium.* An amount of methanol not to exceed 2% of the total volume of the Standard solution may be used to dissolve the amiloride hydrochloride.~~

■Calculate the amount of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$) dissolved, in percentage, by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from *Test solution 1* and the *Amiloride standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Amiloride standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg, of amiloride.

Correction for the interference of amiloride is made using the following equation:

$$A_{UC} = A_{U270} - \left[\frac{F \times A_{U363}}{5}\right]$$

in which A_{UC} is the corrected absorbance of *Test solution 1* at 270 nm; A_{U270} is the absorbance of *Test solution 2* at 270 nm; A_{U363} is the absorbance of *Test solution 1* at 363 nm; and *F* is as defined below.

$$F = \frac{A_{SAmiloride}\ at\ 270\,nm}{A_{SAmiloride}\ at\ 363\,nm}$$

in which $A_{SAmiloride}$ is the absorbance of the *Amiloride standard solution.*

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Calculate the amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved, in percentage, by the formula:

$$\frac{A_{UC} \times C_S \times 900 \times \left(\frac{25}{5}\right) \times 100}{A_S \times LC}$$

in which A_{UC} is the corrected absorbance of *Test solution 1* at 270 nm; A_S is the absorbance of the *Hydrochlorothiazide standard solution;* C_S is the concentration, in mg per mL, of the *Hydrochlorothiazide standard solution;* 900 is the volume, in mL, of *Medium;* (25/5) is the dilution factor of *Test solution 2;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg, of hydrochlorothiazide. ■2S (*USP29*)

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_6H_8ClN_7O \cdot HCl$ and 75% *(Q)* of the labeled amount of $C_7H_8ClN_3O_4S_2$ are dissolved in 30 minutes.

BRIEFING

Amoxicillin and Clavulanate Potassium for Oral Suspension, *USP 28* page 147. It is proposed to delete the test for *Water* to be in accordance with the approved NDA of this drug product.

(PA7a: B. Gilbert) RTS—42078-1

Delete the following:

~~■**Water,** *Method I* ⟨921⟩: not more than 7.5% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is less than 40 mg per mL; not more than 8.5% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is equal to or more than 40 mg per mL and is less than or equal to 50 mg per mL; not more than 11.0% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is more than 50 mg per mL and is less than or equal to 80 mg per mL; and not more than 12.0% where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is more than 80 mg per mL.~~ ■2S (*USP29*)

BRIEFING

Aspirin Boluses, *USP 28* page 180. It is proposed to make some modifications in the *Dissolution* test. Aspirin Boluses are very large tablets weighing approximately 20 g. Therefore, it is proposed to replace *Apparatus 1* with *Apparatus 2* to accommodate these large tablets. The rotation speed is being set at 75 rpm to improve the dispersion of the particles. The *Medium* is being changed to 900 mL of 0.5 M phosphate buffer, pH 7.4, to provide and maintain sink conditions.

(BPC: M. Marques) RTS—41253-1; 42511-1

Change to read:

Dissolution ⟨711⟩—

Medium: ~~0.05 M acetate buffer, prepared by mixing 8.97 g of sodium acetate trihydrate with 2700 mL of water, adjusting with glacial acetic acid to a pH of 4.50 ± 0.05, and diluting with water to 3000 mL, and mixing; 500 mL.~~

■0.5 M phosphate buffer, pH 7.4; 900 mL. ■2S (*USP29*)

~~*Apparatus 1* [NOTE—Use basket and shaft dimensions that accommodate the size of the individual bolus.]: 100 rpm.~~

■*Apparatus 2:* 75 rpm. ■2S (*USP29*)

Time: 45 minutes.

Diluting solution—Prepare a mixture of acetonitrile and formic acid (99 : 1).

Procedure—Determine the amount of aspirin ($C_9H_8O_4$) dissolved from UV absorbances at the wavelength of the isosbestic point of aspirin and salicylic acid at 265 ± 2 nm of filtered portions of the solution under test, suitably diluted with *Diluting solution*, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same medium. [NOTE—Prepare the Standard solution at the time of use.]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_9H_8O_4$ is dissolved in 45 minutes.

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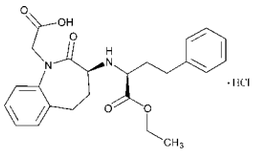
BRIEFING

Benazepril Hydrochloride, page 1422 of *PF* 29(5) [Sept.–Oct. 2003]. On the basis of comments received, it is proposed to make changes in the *Absorbance of solution* section to use a standard 1-cm spectrophotometric cell. The *Loss on drying* limit is also being revised to 1.5%.

(PA5: A. Wilk) RTS—41987-1

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~~ 1-cm cell at 420 nm, is not more than ~~0.03,~~ 0.015, methanol being used as the blank.

Absorptivity—

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%~~ 1.5% of its weight.

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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 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*

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~~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. Chromatograph 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

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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 compounds 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 USP 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*)-~~

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~~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 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-ethoxycarbonyl-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*~~ is the peak response for each impurity obtained from the *Test solution;* and *r*~~ 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

Benazepril Related Compound	Relative Retention Time	Limit (%)
E[1]	0.4	0.2
F[2]	0.5	0.2
C[3]	0.6	0.3
B[4]	1.5	0.5
D[5]	1.7	0.2
G[6]	2.0	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 (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.

In-Process Revision

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 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 *(USP29)*

BRIEFING

Betamethasone Oral Solution, *USP 28* page 242. In the *Thin-layer chromatographic identification test*, it is proposed to reduce the volume of *Assay preparation* taken to prepare the *Test solution* from 25 mL to 1 mL.

(PA1: C. Anthony) RTS—42595-2

Betamethasone Oral Solution

Former title: Betamethasone Syrup

Change to read:

Thin-layer chromatographic identification test ⟨201⟩—
Test solution—Evaporate ~~25 mL~~

■1 mL■2S *(USP29)* 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.

BRIEFING

Biphasic Isophane Insulin Human Suspension. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(BNT: L. Callahan) RTS—41466-1; 41896-1; 42154-1; 42264-2

In-Process Revision

Add the following:

■Biphasic Isophane Insulin Human Suspension

» Biphasic Isophane Insulin Human Suspension is a sterile buffered suspension of Insulin Human, complexed with Protamine Sulfate, in a solution of Insulin Human. Its potency, based on the sum of its insulin and desamido insulin components, as determined in the *Assay*, is not less than 95.0 percent and not more than 105.0 percent of the potency stated on the label, expressed in USP Insulin Human Units in each mL.

Packaging and storage—Preserve in the unopened, multiple-dose container provided by the manufacturer. Store in a refrigerator, protect from sunlight, and avoid freezing.

Labeling—The Suspension container label states that the Suspension is to be properly resuspended before use. Label it to indicate that it has been prepared with Insulin Human of semisynthetic origin (i.e., derived by enzyme modification of pork pancreas insulin) or with Insulin Human of recombinant DNA origin (i.e., obtained from microbial synthesis), whichever is applicable. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. The label states the potency in USP Insulin Human Units per mL and the percent ratio of isophane insulin human suspension to soluble insulin human injection.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Insulin Human 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 80 USP Endotoxin Units per 100 USP Insulin Human Units.

Sterility ⟨71⟩—It meets the requirements of the test for *Sterility* under *Isophane Insulin Suspension.*

pH ⟨791⟩**:** between 7.0 and 7.8, determined potentiometrically.

Zinc content ⟨591⟩**:** between 0.02 mg and 0.04 mg for each 100 USP Insulin Human Units.

Limit of high molecular weight proteins—Proceed as directed in the test for *Limit of high molecular weight proteins* under *Insulin Injection*: not more than 3.0% is found.

Soluble insulin human content—[NOTE—Use one of the two methods listed below.]

METHOD 1—

Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Insulin.*

Soluble insulin test solution—Maintain the temperature at 25 ± 1° throughout the procedure. Transfer 5.0 mL of the Suspension to a centrifuge tube. Add 20 µL of 1 N sodium hydroxide, and adjust with 0.05 N hydrochloric acid or 0.05 N sodium hydroxide to a pH of 8.20 ± 0.02 if the total zinc concentration is approximately 20 µg per mL or adjust to a pH of 8.35 ± 0.02 if the total zinc concentration is approximately 30 µg per mL. Record the volume, in µL, of acid or base needed to adjust the pH. Mix, and allow to stand for 1 hour. Centrifuge, transfer the supernatant to another centrifuge tube, and repeat the centrifugation. Transfer 2 mL of the supernatant to another tube, add 5 µL of 9.6 N hydrochloric acid, and mix.

Total insulin test solution—Transfer 2 mL of Suspension to a suitable vessel, add 5 µL of 9.6 N hydrochloric acid, and allow the suspension to clarify. Dilute the resulting solution with 0.01 N hydrochloric acid to the same theoretical con-

centration of insulin as the *Soluble insulin test solution* (e.g., if the Suspension is labeled to contain 20% soluble insulin, the dilution factor is 100/20 = 5).

Procedure—Separately inject equal volumes (about 20 µL) of the *Soluble insulin test solution* and *Total insulin test solution* into the chromatograph, record the chromatograms, and measure the human insulin peak responses. Calculate the amount of soluble insulin human as a percent of the total insulin content of the Suspension by the formula:

$$(100/D)[(5020 + V_A)/5000](r_S / r_T)$$

in which D is the dilution factor for the *Total insulin test solution;* V_A is the number of µL added to adjust the pH of the *Soluble insulin test solution;* and r_S and r_T are the responses of the *Soluble insulin test solution* and the *Total insulin test solution*, respectively. The percent of soluble insulin human is in the range $L \pm 5$, where L is the percent of soluble insulin human stated on the product label.

METHOD 2—

Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Insulin.*

0.1 M Tris buffer solution—Dissolve 3.54 ± 0.01 g of Tris(hydroxymethyl)aminomethane hydrochloride and 3.34 ± 0.01 g of Tris(hydroxymethyl)aminomethane in 500 mL of water. The pH of the *0.1 M Tris buffer solution* must be between 8.0 and 8.4. If the pH is outside of this range, discard the solution and prepare fresh; do not adjust the pH. [NOTE—This solution is stable for two weeks and should be stored out of direct sunlight.]

Soluble insulin test solution—Thoroughly mix 2.0 mL of Suspension with 2.0 mL of *0.1 M Tris buffer solution*. Immerse the container in a water bath at 25 ± 2° for 30 ± 2 minutes. Immediately pass this solution through a 0.2-µm filter using a disposable syringe. Transfer 2 mL of the filtrate to a suitable vessel, and add 1 mL of 0.2 N hydrochloric acid and 2 mL of 0.01 N hydrochloric acid.

Total insulin test solution—For each mL of Suspension, add 3.0 µL of 9.6 N hydrochloric acid, mix, and allow the suspension to clarify. Dilute the resulting solution with 0.01 N hydrochloric acid to the same theoretical concentration of insulin as the *Soluble insulin test solution* (e.g., if the product is labeled to contain 20% soluble insulin, the dilution factor is 2/1 × 5/2 × 100/20 = 25).

Procedure—Separately inject equal volumes (about 20 µL) of the *Soluble insulin test solution* and the *Total insulin test solution,* record the chromatograms, and measure the human insulin peak responses. Calculate the amount of soluble insulin human as a percent of the total human insulin content of the Suspension by the formula:

$$(500/D)(r_S / r_T)$$

in which D is the dilution factor for the *Total insulin test solution;* and r_S and r_T are the human insulin peak responses obtained from the *Soluble insulin test solution* and the *Total insulin test solution*, respectively. The percent of soluble insulin human is in the range $L \pm 5$, where L is the percent of soluble insulin human stated on the product label.

Assay—Proceed as directed in the *Assay* under *Insulin Human Injection.*■2S (*USP29*)

In-Process Revision

BRIEFING

Bismuth Subsalicylate Oral Suspension, page 1166 of *PF* 30(4) [July–Aug. 2004]. On the basis of comments received, it is proposed to eliminate the requirement for absence of *Salmonella* species in the test for *Microbial limits.*

(PA2: C. Anthony) RTS—42669-1

Add the following:

■Bismuth Subsalicylate Oral Suspension

» Bismuth Subsalicylate Oral Suspension is a suspension that contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_7H_5BiO_4$. It may contain one or more suitable buffers, coloring agents, flavors, preservatives, stabilizers, sweeteners, and suspending agents.

Packaging and storage—Preserve in tight containers, and avoid freezing. Store between 15° and 30°.

Identification—

A: It meets the requirements of the tests for *Bismuth* ⟨191⟩.

B: It meets the requirements of the tests for *Salicylate* ⟨191⟩, after acidifying with nitric acid.

pH ⟨791⟩**:** between 3.0 and 5.0.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 100 cfu per g, the combined yeast and mold count does not exceed 50 cfu per g, and it meets the requirements of the tests for absence of *Escherichia coli.* ~~and of *Salmonella* species.~~

Assay—

Standard preparation—Transfer about 500 mg of bismuth metal, accurately weighed, into a 200-mL volumetric flask, dissolve in 12 mL of nitric acid, and dilute with 0.01 N nitric acid to volume. Transfer 10.0 mL of this solution into a 500-mL volumetric flask, and dilute with 1 N nitric acid to volume to obtain a solution having a concentration of 50 µg of bismuth per mL.

Assay preparation—Transfer an accurately measured quantity of about 10 g of Oral Suspension, previously well-shaken in its original container to ensure homogeneity, to a 200-mL volumetric flask. Add about 100 mL of 1 N nitric acid, mix, and dilute with 1 N nitric acid to volume. Mix well without shaking, and transfer 10.0 mL of this mixture into a 100-mL volumetric flask, and dilute with 1 N nitric acid to volume. Centrifuge about 20 mL at 4500 rpm for at least 10 minutes.

Procedure—Transfer an accurately measured volume of the *Assay preparation* that contains about 0.9 mg of bismuth subsalicylate and 10 mL of the *Standard preparation* to separate 50-mL volumetric flasks. Add 10.0 mL of 10% ascorbic acid solution and 25.0 mL of 20% potassium iodide solution into each volumetric flask, dilute with water to volume, and mix well. Concomitantly determine the absorbances of both solutions in 1.0-cm cells at a wavelength of 463 nm with a suitable spectrophotometer using the reagent blank to set the spectrophotometer. Calculate the quantity, in mg, of $C_7H_5BiO_4$ in the portion of Oral Suspension taken by the formula:

$$(362.11/208.98)20(C/V)(A_U/A_S)$$

in which 362.11 and 208.98 are the molecular weights of bismuth subsalicylate and bismuth, respectively; C is the concentration, in µg per mL, of bismuth in the *Standard preparation;* V is the volume, in mL, of the *Assay prepara-*

tion taken; and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

BRIEFING

Calcitonin Salmon, page 385 of *PF* 31(2) [Mar.–Apr. 2005]. On the basis of comments received, it is proposed to delete several tests that are process-specific and not product-specific. It is proposed to delete (1) *Identification* test *B* (UV absorption) because it is thought that the retention times from the *Assay* and the *Amino acid profile* are sufficient for identification and (2) the correction factors for threonine and serine in the test for *Amino acid profile* because it is believed that the acceptance criteria are wide enough to account for any degradation that occurs during hydrolysis. It is also proposed to add a test for *Organic volatile impurities.* In addition, minor editorial changes have been made.

(BNT: L. Callahan) RTS—42620-1; 42662-1

Add the following:

■Calcitonin Salmon

$C_{145}H_{240}N_{44}O_{48}S_2$ 3432 daltons [*47931-85-1*].

» Calcitonin Salmon is a synthetic polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It lowers the calcium concentration in the plasma of mammals by diminishing the rate of bone resorption. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid–free and dried basis.

NOTE—One mg of acetic acid–free, anhydrous Calcitonin Salmon is equivalent to 6000 USP Calcitonin Salmon Units.

Packaging and storage—Preserve in tight containers. Store in a refrigerator, protected from light.

Labeling—The labeling states that the material is synthetic.

USP Reference standards ⟨11⟩—*USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS* (*N*-acetyl-cys[1]-calcitonin). ~~*USP Endotoxin RS.*~~

Identification—

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

~~**B: The UV absorption spectrum of a 0.1% solution (based on free peptide) in 0.01 N hydrochloric acid exhibits a minima and a maxima at the same wavelengths as those of a similar solution of USP Calcitonin Salmon RS, concomitantly measured. The absorbance at approximately 275 nm (maxima) is about 0.40 to 0.55, and the ratio of the absorbance at 275 nm (maxima) and 254 nm (minima) is between 1.6 and 2.5.~~**

Amino acid profile (see *Amino Acid Analysis* ~~*Method 1,*~~ under *Biotechnology-Derived Articles—Tests* ⟨1047⟩)—[NOTE—The concentration of amino acids in the *Internal standard solution,* the *Standard amino acid solution,* and the *Standard solution* and the amount of material used to prepare the *Test solution* can be adjusted depending on the method used for amino acid analysis. The concentrations given are based on analysis using *Method 1.*]

Internal standard solution—Prepare a 1-mM solution of γ-aminobutyric acid.

In-Process Revision

Standard amino acid solution—Prepare a mixture containing equimolar amounts of ammonia and the L form of lysine, histidine, arginine, aspartic acid, threonine, serine, proline, valine, glutamic acid, glycine, leucine, and tyrosine, together with half the equimolar amount of L-cystine, in 0.1 M hydrochloric acid. The final concentration is about 2.5 mM for each amino acid.

Standard solution—Transfer 5 mL of the *Internal standard solution* and 2 mL of the *Standard amino acid solution* into a 50-mL volumetric flask, and dilute with 0.1 M hydrochloric acid to volume.

Test solution—Place about 1.5 mg of an accurately weighed quantity of Calcitonin Salmon into a heavy-wall ignition tube, add 1.0 mL of 6 N hydrochloric acid, allow to cool, immerse the lower half of the tube in a freezing mixture until the contents are frozen, evacuate to approximately 10 μM, purge with nitrogen (repeat the evacuation and nitrogen purge three times), and seal the tube while it is under a 10-μM vacuum. Heat for 16 hours at 110° to 115° in an air oven. Cool, open the tube, dry in a vacuum desiccator, remove the contents, and allow to cool to room temperature. Dissolve in 0.1 M hydrochloric acid, transfer to a 10-mL volumetric flask, add 1 mL of *Internal standard solution,* and dilute with 0.1 M hydrochloric acid to volume.

Procedure—Standardize the amino acid analyzer, using the *Standard solution.* Inject the *Test solution* into the amino acid analyzer, and determine the relative proportion of amino acids.

Calculation of amino acid profile—Express the content of each amino acid in moles, using an internal standard calibration technique. Calculate the relative proportions of the amino acids by taking as equivalent to 1 the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, valine, leucine, histidine, arginine, and lysine divided by 20. ~~For threonine and serine, perform the same calculation, and correct the concentrations for degradation by adding 5% and 10%, respectively, to their indicated results.~~ The requirements are met if the values fall within the following limits: aspartic acid, 1.8 to 2.2; glutamic acid, 2.7 to 3.3; proline, 1.7 to 2.3; glycine, 2.7 to 3.3; valine, 0.9 to 1.1; leucine, 4.5 to 5.3; histidine, 0.9 to 1.1; arginine, 0.9 to 1.1; lysine, 1.8 to 2.2; serine, 3.2 to 4.2; threonine, 4.2 to 5.2; tyrosine, 0.7 to 1.1; half cystine, 1.4 to 2.1.

~~**Bacterial endotoxins** ⟨85⟩—It contains not more than 1000 USP Endotoxin Units per mg of calcitonin salmon.~~

Microbial limits ⟨61⟩—The test is performed on a portion of about 0.2 g, accurately weighed. The total aerobic microbial count does not exceed 100 cfu per g. ~~It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*~~

~~**pH** ⟨791⟩**:** between 4.0 and 6.0 in a 1% solution in carbon dioxide–free water.~~

Water, *Method Ic* ⟨921⟩**:** not more than 10%.

Heavy metals, *Method II* ⟨231⟩**:** 0.005%.

~~**Limit of trifluoroacetic acid**—[NOTE—Use deionized, degassed water where water is indicated.]~~

~~*Solution A:* water.~~

~~*Solution B:* 0.005 N sodium hydroxide.~~

~~*Solution C:* 0.1 N sodium hydroxide.~~

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

In-Process Revision

Chloride stock standard solution— Dissolve an accurately weighed quantity of sodium chloride in water to obtain a solution having a concentration of the chloride ion of about 0.1 mg per mL.

Trifluoroacetic acid stock standard solution— Dissolve an accurately weighed quantity of trifluoroacetic acid in water to obtain a solution having a concentration of trifluoroacetic acid of about 0.1 mg per mL.

Resolution solution— Pipet 0.2 mL of *Chloride stock standard solution* and 0.5 mL of *Trifluoroacetic acid stock standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution that contains 0.2 µg of chloride and 0.5 µg of trifluoroacetate per mL, respectively.

Standard solutions— Pipet 0.2 mL, 0.5 mL, 1.0 mL, and 2.0 mL of *Trifluoroacetic acid stock standard solution* into ordered 100-mL volumetric flasks. Dilute with water to volume and mix to obtain solutions that contain concentrations of about 0.2 µg, 0.5 µg, 1.0 µg, and 2.0 µg of trifluoroacetate per mL, respectively.

Test solution— Transfer about 10 mg of Calcitonin Salmon, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The ion chromatograph is equipped with a conductivity detector, a 4-mm × 5-cm anion exchange guard column containing packing L31, a 4-mm × 25-cm anion exchange analytical column containing packing L31, a high capacity anion trap column in hydroxide form in the eluant line in front of the injection valve, and a micromembrane anion self regenerating suppressor. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–2	90	10	0	isocratic
2–5	90 →0	10 →100	0	linear gradient
5–15	0	100 →65	0 →35	linear gradient
15–20	0 →90	65 →10	35 →0	linear gradient

Chromatograph the *Resolution solution,* and record the peak responses as directed for the *Procedure*: the resolution, *R,* between the chloride peak and the trifluoroacetic acid peak is not less than 3; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure— Separately inject equal volumes (about 100 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area of peak responses. Plot the response of the trifluoroacetic acid peak in the *Standard solutions* versus the concentration of trifluoroacetic acid, and draw the straight line best fitting the plotted points. From the graphs so obtained, determine a concentration value, *C,* in µg per mL for trifluoroacetic acid. Calculate the quantity, in ppm, for trifluoroacetic acid in Calcitonin Salmon by the formula:

$$5000(C/W),$$

in which *W* is the weight in mg of Calcitonin Salmon taken to prepare the *Test solution:* not more than 200 ppm of trifluoroacetic acid is found.

Limit of residual solvents—

Standard stock solution— Prepare a solution containing about 300 µg of methanol, 40 µg of acetonitrile, 60 µg of methylene chloride, 500 µg of *tert* butyl methyl ether, and 90 µg of dimethylformamide per mL of methyl sulfoxide.

In-Process Revision

~~*Standard solution*—Transfer 5 mL of the *Standard stock solution* to a 25-mL volumetric flask, and dilute with dimethyl sulfoxide to volume. Transfer 1 mL of the *Standard solution* to a 20-mL headspace vial fitted with a septum and a crimp cap, and seal the vial.~~

~~*Test solution 1*—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of dimethyl sulfoxide, seal the vial, and mix.~~

~~*Test solution 2*—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of *Standard solution,* seal the vial, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame ionization detector and contains a 0.32-mm × 60-m fused silica column coated with a 1.0-µm film of stationary phase G38. Nitrogen is used as the carrier gas, flowing at a rate of about 25 mL per minute. The column temperature is maintained at 45° for 2 minutes, then increased at a rate of 10° per minute to 75°, then increased at a rate of 5° per minute to 170° and maintained at 170° for 3 minutes. The split injector temperature is maintained at about 200°, and the detector temperature is maintained at about 170°. The transfer loop and transfer line temperature is 170°, and the pressurize time is 0.5 minute. The *Standard solution* vial and the *Test solutions 1* and *2* vials are maintained at about 90°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.55 for methanol, 0.76 for acetonitrile, 1.0 for methylene chloride, 1.2 for *tert* butyl methyl ether, and 2.3 for dimethylformamide; and the relative standard deviation, determined from peak areas for each peak, for six replicate injections is not more than 10%.~~

~~*Procedure*—Separately inject equal volumes (about 1 mL) of headspace from vials of *Test solution 1* and *Test solution 2* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of methanol, acetonitrile, methylene chloride, *tert* butyl methyl ether, and dimethylformamide in the Calcitonin Salmon taken by the formula:~~

$$~~100(r_{U1})(C)/(r_{S1})(W_{U1}) - (r_{U1})(W_{U2})~~,$$

~~in which C is the concentration, in mg per mL, of the relevant analyte in the *Standard solution;* W_{U1} and W_{U2} are the weights, in mg, of Calcitonin Salmon taken to prepare *Test solution 1* and *Test solution 2,* respectively; and r_{U1} and r_{U2} are the peak areas of the corresponding analyte obtained from *Test solution 1* and *Test solution 2,* respectively: not more than 3000 µg of methanol, 400 µg of acetonitrile, 600 µg of methylene chloride, 5000 µg of *tert* butyl methyl ether, and 900 µg of dimethylformamide per g of Calcitonin Salmon are found.~~

Organic volatile impurities ⟨467⟩: meets the requirements.

Acetic acid content—

Internal standard stock solution—Mix 1 mL of dioxane with water to obtain 100 mL of solution.

Standard solution—Transfer approximately 100 mg of glacial acetic acid, accurately weighed, and 10 mL of *Internal standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 10-mL volumetric flask, add 1 mL of *Internal standard stock solution,* dissolve in and dilute with water to volume, and mix.

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 3-m glass column packed with 10% liquid phase G35, 1% phosphoric acid, on support S1A. Nitrogen is the carrier gas, flowing at a rate of about 30 mL per minute. The column temperature is maintained at 70° for 4 minutes, then increased at a rate of 8° per minute to 120°, then maintained at 120° for 4 minutes. The injection port and detector temperatures are maintained isothermally at about 200°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between dioxane and acetic acid is not less than 8; and the relative standard deviation for replicate injections is not more than 5.0%.

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 responses for the major peaks. The retention times are about 3 minutes for acetic acid and 1 minute for dioxane. Calculate the percentage of acetic acid in the portion of Calcitonin Salmon taken by the formula:

$$1000(C/W)(R_U / R_S)$$

in which C is the concentration, in mg per mL, of acetic acid in the *Standard solution; W* is the weight, in mg, of Calcitonin Salmon used to prepare the *Test solution,* and R_U and R_S are the peak response ratios of acetic acid to dioxane obtained from the *Test solution* and the *Standard solution,* respectively: not less than 4.0% and not more than 15.0% is found.

Bioidentity—

RPMI 1640 with L-glutamine—Prepare a mixture of the ingredients in the quantities shown in sufficient water to obtain 1 L of medium, and sterilize by filtration.

Calcium Nitrate	100.00 mg
Potassium Chloride	400.00 mg
Magnesium Sulfate, Anhydrous	48.84 mg
Potassium Chloride	400 mg
Sodium Chloride	6000 mg
Sodium Phosphate, Dibasic, Anhydrous	800 mg
Sodium Bicarbonate	2000 mg
Glycine	10 mg
L-Arginine	200 mg
L-Asparagine	50 mg
L-Aspartic Acid	20 mg
L-Cystine Dihydrochloride	65 mg
L-Glutamic Acid	20 mg
L-Glutamine	300 mg
L-Histidine	15 mg
L-Hydroxyproline	20 mg
L-Isoleucine	50 mg
L-Leucine	50 mg
L-Lysine Hydrochloride	40 mg
L-Methionine	15 mg
L-Phenylalanine	15 mg
L-Proline	20 mg
L-Serine	30 mg
L-Threonine	20 mg
L-Tryptophan	5 mg
L-Tyrosine Disodium Salt Dihydrate	29 mg
L-Valine	20 mg
Biotin	0.2 mg
Choline Chloride	3 mg
D-Calcium Pantothenate	0.25 mg
Folic Acid	1 mg
i-Inositol	35 mg
Niacinamide	1 mg
Para-Aminobenzoic Acid	1 mg
Pyridoxine Hydrochloride	1 mg

Riboflavin	0.2 mg
Thiamine Hydrochloride	1 mg
Vitamin B_{12}	0.005 mg

Medium A (growth medium)—Using aseptic technique, prepare the following tissue culture medium.

RPMI 1640 with L-glutamine	500 mL
Fetal bovine serum	50 mL
1 M HEPES	5 mL
Penicillin/streptomycin solution (10,000 IU per mL /10 mg per mL)	5 mL
Human insulin	10 IU
Hydrocortisone	0.5 mg

Medium B (stimulation medium)—Dissolve 5 g of albumin bovine serum (BSA) in 500 mL of 2 mM *RPMI 1640 with L -glutamine.*

2% BSA solution—Dissolve 50 mg of albumin bovine serum in 25 mL of water. [NOTE—Use within 1 day.]

Formic acid/BSA solution—Add 25 mL of 0.1 M formic acid and 5 mL of *2% BSA solution* to a 50-mL volumetric flask, and dilute with water to volume. [NOTE—Use within 2 days.]

Trypsin–tetrasodium ethylenediaminetetraacetate (EDTA) solution—Prepare a sterile filtered solution containing 0.25% trypsin and 0.53 mM EDTA.

Dulbecco's phosphate buffered saline—Dissolve 8 g of sodium chloride, 1.15 g of dibasic sodium phosphate, 0.2 g of monobasic potassium phosphate, 0.2 g of potassium chloride, 0.1 g of calcium chloride, and 0.1 g of magnesium chloride in 1 L of water.

Standard stock solution—Dissolve an accurately weighed quantity of USP Calcitonin Salmon RS in *Formic acid/BSA solution* to obtain a solution having a known concentration of about 20 µg per mL.

Positive control solution—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 1 ng per mL.

Negative control solution: Medium B.

Standard solution A—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.1 ng per mL.

Standard solution B—Dilute *Standard solution A* quantitatively with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.033 ng per mL.

Standard solution C—Dilute *Standard solution B* quantitatively (1 : 2) with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.011 ng per mL.

Standard solution D—Dilute *Standard solution C* quantitatively (1 : 2) with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.0037 ng per mL.

Test stock solution—Dissolve an accurately weighed quantity of Calcitonin Salmon in *Formic acid/BSA solution* to obtain a solution having a concentration of about 20 µg per mL.

Test solution A—Quantitatively dilute the *Test stock solution* with *Medium B* to obtain a solution of Calcitonin Salmon having a concentration of 0.1 ng per mL.

Test solution B—Quantitatively dilute *Test solution A* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.033 ng per mL.

Test solution C—Quantitatively dilute *Test solution B* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.011 ng per mL.

Test solution D—Quantitatively dilute *Test solution C* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.0037 ng per mL.

Cell culture preparation—Prepare cell culture of the human mammary tumor cell line T-47D. Cells are propagated using *Medium A* at 37° and 5% carbon dioxide. The medium is changed every 2 days, and cells are passaged every 5 to 9 days, using *Trypsin–EDTA solution* with a 1 : 4 subculture.

Cell suspension—For the test, use a cell culture that is 5 to 9 days old. Remove the cell culture medium from the flask by aspiration, add 10 mL of *Dulbecco's phosphate buffered saline,* and rock the culture flask to rinse the entire monolayer. Remove the liquid by aspiration, add 2 mL of *Trypsin–EDTA solution,* spread over the entire monolayer, allow to stand for 3 to 5 minutes, and add 10 mL of *Medium A.* Homogenize the cell suspension using a pipet, transfer to a 15-mL polypropylene tube, centrifuge at about 220 × *g* for 5 minutes, pour off the supernatant, and resuspend the cell pellet in 10 mL of *Medium A.* Count the cells, and adjust the cell density through dilution, using *Medium A,* to 2.5×10^4 cells per mL.

Procedure—Place 200 µL of the *Cell suspension* into each well of a 96-well culture plate (the *tissue culture plate*), and incubate for 18 to 24 hours at 37° and 5% carbon dioxide. Fill each well of an empty round-bottomed 96-well culture plate (the *prepared plate*) with 150 µL of one of the following solutions: *Positive control solution, Negative control solution, Standard solutions A–D,* and *Test solutions A–D,* so that each solution fills at least five wells on the prepared plate. After incubation, remove the culture medium from the tissue culture plate. Using an 8-channel or 12-channel pipet, rapidly transfer 100 µL of solution from each well of the prepared plate to each well of the tissue culture plate. Incubate for 15 minutes at ambient temperature, remove the solution from each well, stop stimulation by immediately adding an appropriate cell-lysis buffer, and quantitate cAMP produced within the cells, using a validated kit. Perform the test three times, using three different 96-well culture plates. [NOTE—Some kits include a cell-lysis reagent and a sequestering agent for the cell-lysis reagent. The range of the test kit is between 0.05 ng and 10 ng per mL of cAMP. The number of cells used in the assay may vary depending on the validated kit used to quantitate cAMP.] Potency is determined by a 3-dose, 6-point parallel-line assay, using standard statistical methods. The calculation is carried out using both the lower three concentrations and the upper three concentrations. For the assay to be valid, the requirements for regression and parallelism must be met. If the requirements for validity are met to the same extent in both assessments (the lower and the higher assessments), the final result is determined from the concentration range that shows the higher value when the common slope is divided by the mean square error. The potency levels determined from all three performances of the test are homogeneous, and the confidence limits for all three determinations are between 64% and 156% of the calculated potency.

Related peptides and other related substances—

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

Solution A, Solution B, Mobile phase, Resolution solution, and *Chromatographic system*—Prepare 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 area percentage of each peak observed in the chromatogram. Disregard any peaks due to the solvent and any peaks whose area is less than 0.1% of the principal peak. No peak other than the principal peak constitutes more than 3.0% of the total

area of all peaks. The sum of the areas of all the peaks apart from the principal peak is not greater than 5.0% of the sum of the areas of all the peaks including the principal peak.

Other requirements—Where the label states that Calcitonin Salmon is sterile, it meets the requirements for *Sterility* under *Calcitonin Salmon Injection.*

Assay—

Solution A—Dissolve ~~3.62~~ 3.26 g of tetramethylammonium hydroxide pentahydrate in 900 mL of water, add 100 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, and degas.

Solution B—Dissolve 1.45 g of tetramethylammonium hydroxide pentahydrate in 400 mL of water, add 600 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, 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⟩).

Standard preparation—Transfer about 10.0 mg of USP Calcitonin Salmon RS, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

Resolution solution—Dissolve the contents of a vial of USP Calcitonin Salmon Related Compound A RS in 0.4 mL of *Solution A,* add 0.1 mL of the *Standard preparation,* and mix.

Assay preparation—Transfer about 10.0 mg of Calcitonin Salmon, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A,* 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 packing L1. The column temperature is maintained at about 65°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–30	72→48	28→52	linear gradient
30–32	48→72	52→28	linear gradient
32–55	72	28	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.15 for calcitonin salmon related compound A and 1.0 for calcitonin salmon; the resolution, *R,* between calcitonin salmon related compound A and calcitonin salmon is not less than 3; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 3%.

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 of the major peaks. Calculate the percentage of calcitonin salmon in the portion of Calcitonin Salmon taken by the formula:

$$P(W_S / W_U)(r_U / r_S)$$

in which P is the percentage of calcitonin salmon in USP Calcitonin Salmon RS; W_S is the weight, in mg, of USP Calcitonin Salmon RS taken to prepare the *Standard preparation;* W_U is the weight, in mg, of Calcitonin Salmon used to prepare the *Assay preparation;* and r_U and r_S are the main peak areas from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

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BRIEFING

Carbamazepine Tablets, *USP 28* page 342 and the *Second Interim Revision Announcement* on page 320 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to delete *Dissolution Test 4* from this monograph because the test was assigned to a chewable tablet product that now complies with *Dissolution Test 1*.

(BPC: M. Marques) RTS—42521-1

Change to read:

Dissolution ⟨711⟩—

FOR PRODUCTS LABELED AS 100-MG CHEWABLE TABLETS:

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: water containing 1% sodium lauryl sulfate; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 288 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.[NOTE—A volume of methanol not exceeding 1% of the final total volume of the Standard solution may be used to dissolve the carbamazepine.]

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use *Acceptance Table 1* under *Dissolution* ⟨711⟩, with the following exceptions: at S_2, no unit is less than Q – 5%; at S_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

~~TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.~~

~~*Medium:* 0.1 N hydrochloric acid containing 1% sodium lauryl sulfate; 225 mL. Add 2 drops of simethicone to each.~~

~~*Apparatus 3* (see *Drug release* ⟨724⟩): 35 dips per minute; use 20-mesh screen on the top of the reciprocating cylinder and a 100-mesh screen on the bottom of the reciprocating cylinder.~~

~~*Time:* 60 minutes.~~

~~*Procedure*—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.~~

~~*Tolerances*—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes, the acceptance criteria specified for *Test 1* being used.~~

■■2S (*USP29*)

FOR PRODUCTS LABELED AS 200-MG TABLETS:

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances*—Between 45% and 75% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use *Acceptance Table 1* under *Drug Release* ⟨724⟩, with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances*—Between 60% and 85% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use *Acceptance Table 1* under *Drug Release* ⟨724⟩, with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

Change to read:

Dissolution ⟨711⟩—

FOR PRODUCTS LABELED AS 100-MG CHEWABLE TABLETS—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

Medium: water containing 1% sodium lauryl sulfate; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 288 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*. [NOTE—A volume of methanol not exceeding 1% of the final total volume of the Standard solution may be used to dissolve the carbamazepine.]

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 1*,•$_2$ with the following exceptions: at S_2, no unit is less than Q – 5%; at S_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

~~TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.~~

~~*Medium:* 0.1 N hydrochloric acid containing 1% sodium lauryl sulfate; 225 mL. Add 2 drops of simethicone to each.~~

~~*Apparatus 3:* •$_2$ 35 dips per minute; use 20-mesh screen on the top of the reciprocating cylinder and a 100-mesh screen on the bottom of the reciprocating cylinder.~~

~~*Time:* 60 minutes.~~

~~*Procedure*—Determine the amount of $C_{15}H_{12}N_2O$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 284 nm on filtered portions of the solution under test, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Carbamazepine RS in the same *Medium*.~~

~~*Tolerances*—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes, the acceptance criteria specified for *Test 1* being used.~~

■■2S (*USP29*)

FOR PRODUCTS LABELED AS 200-MG TABLETS—

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances:* between 45% and 75% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 2*,•$_2$ with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated

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range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, *Apparatus*, and *Procedure*—Proceed as directed for *Test 1*.

Times and *Tolerances:* between 60% and 85% of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 15 minutes; not less than 75% *(Q)* of the labeled amount of $C_{15}H_{12}N_2O$ is dissolved in 60 minutes. Use •*Acceptance Table 2,*•2 with the following exceptions: at 15 minutes—at L_2, no unit is more than 5% outside the stated range; at L_3, no unit is more than 10% outside the stated range; and not more than 2 of the 24 units are more than 5% outside the stated range. At 60 minutes—at L_2, no unit is less than Q – 5%; at L_3, no unit is less than Q – 10%; and not more than 2 of the 24 units are less than Q – 5%.

•(Official April 1, 2006)•2

BRIEFING

Carbon Dioxide, *USP 28* page 349—See briefing under *Medical Air*.

(AER: K. Zaidi) RTS—42651-2

Change to read:

» Carbon Dioxide contains not less than 99.0 percent, ~~by volume~~

■volume/volume,■2S (*USP29*)
of CO_2.

Change to read:

Packaging and storage—~~Preserve in cylinders.~~

■Preserve in gray cylinders. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)

NOTES—The following tests are designed to reflect the quality of Carbon Dioxide in both its vapor and liquid phases, which are present in previously unopened cylinders. Reduce the container pressure by means of a regulator. Withdraw the specimens for the tests with the least possible release of Carbon Dioxide consistent with proper purging of the sampling apparatus. Measure the gases with a gas volume meter downstream from the detector tubes in order to minimize contamination or change of the specimens. Perform tests in the sequence in which they are listed.

The various detector tubes called for in the respective tests are listed under *Reagent Specifications* in the section *Reagents, Indicators, and Solutions.*

BRIEFING

Cefadroxil for Oral Suspension, *USP 28* page 372. It is proposed to provide an additional *Water* specification for dry preparations that on constitution indicate a content of cefadroxil that is higher than the strengths for which the current 2.0% *Water* limit was established. The original strengths were 25 mg and 50 mg of cefadroxil per mL of suspension (125 mg and 250 mg per 5 mL). The source of much of the water found in these dry preparations is the cefadroxil monohydrate component, which may contain up to 6.0% water. This proposal provides for a *Water* limit of not more than 3.0% where the product is labeled as containing 100 mg of cefadroxil per mL (500 mg per 5 mL) after constitution.

(PA7a: B. Gilbert) RTS— 41870-1

Change to read:

Water, *Method I* ⟨921⟩: not more than 2.0%,

■except where it is labeled as containing 100 mg of cefadroxil per mL after constitution, the limit is not more than 3.0%.■2S (*USP29*)

BRIEFING

Citalopram Tablets, page 745 of *PF* 31(3) [May–June 2005]. It is proposed to add a *Dissolution* test to this new monograph.

(BPC: M. Marques) RTS—41833-7

Add the following:

■Citalopram Tablets

» Citalopram Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of citalopram free base ($C_{20}H_{21}FN_2O$).

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Citalopram Hydrobromide RS. USP Citalopram Related Compound A RS. USP Citalopram Related Compound B RS. USP Citalopram Related Compound C RS. USP Citalopram Related Compound E RS. USP Citalopram Related Compound F RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Extract finely ground Tablet powder containing about 200 mg of citalopram with 30 mL of water, and filter. Add 1 mL of 1 N sodium hydroxide, and extract with 50 mL of cyclohexane by shaking for 10 minutes. Pass the cyclohexane layer through a silicone-treated filter paper into a beaker. Reduce the filtrate down to 3 mL, using gentle heat as necessary. Transfer the hot solution to a small centrifuge tube. Induce crystallization while cooling by scratching the side of the test tube with a spatula. Centrifuge the mixture, and decant off the cyclohexane. Dry the residue under vacuum in a desiccator. Mix approximately 2 mg of the residue with approximately 300 mg of potassium bromide, and record the IR spectrum.

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: A solution of 2 mg per mL equivalent of citalopram in water meets the requirements of the test for *Bromide* ⟨191⟩.

Add the following:

■**Dissolution** ⟨711⟩—

Medium: pH 1.5 buffer (prepared by transferring 118 mL of 1 N hydrochloric acid and 82 mL of 1 N sodium hydroxide to a 1000-mL volumetric flask, diluting with water to volume, and adjusting with 1 N sodium hydroxide to a pH of 1.5); 800 mL, deaerated.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of citalopram hydrobromide dissolved by employing UV absorption at the wavelength of maximum absorbance at about 239 nm on portions of the solution under test passed through a 0.45-µm PVDF filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration (about 12 µg per mL) of USP Citalopram Hydrobromide RS in the same *Medium.* Calculate the amount of citalopram hydrobromide dissolved, in percentage, by the formula:

$$\frac{A_U \times C_S \times 324.44 \times D \times 800 \times 100}{A_S \times 405.30 \times L}$$

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in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the Standard solution; D is the dilution factor of the solution under test; 800 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; 324.44 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; and L is the tablet label claim, in mg, of citalopram.

Tolerances—Not less than 80% (Q) of the labeled amount of citalopram hydrobromide is dissolved in 30 minutes. ■2S (*USP29*)

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Buffer, Diluent, Internal standard solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add 10 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 40 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature. Add a sufficient volume of *Internal standard solution,* and dilute, stepwise if necessary, with *Diluent* to volume to obtain a *Test solution* having a concentration of about 0.1 mg per mL of citalopram and 0.025 mg per mL of internal standard. Pass a portion of this solution through a membrane filter (PVDF) having a 0.45-µm or finer porosity, and use the filtrate.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Procedure—Proceed as directed in the *Assay.* Calculate the quantity, in mg, of $C_{20}H_{21}FN_2O$ in the portion of sample taken by the formula:

$$100(CV)(R_U / R_S)(324.39/405.30)$$

in which C is the concentration, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard solution; V* is the final volume, in mL, required to obtain the *Test solution;* R_U and R_S are the ratio of peak responses of citalopram to the internal standard in the *Test solution* and the *Standard solution,* respectively; and 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively.

Related compounds—

Phosphate buffer—Dissolve 3.15 g of potassium dihydrogen phosphate and 3.60 g of disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) in 1 L of water.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer,* methanol, and acetonitrile (55 : 38 : 7). Adjust with phosphoric acid to a pH of 6.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard solution—Prepare a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard stock solution* with *Mobile phase.*

Sensitivity solution—Prepare a solution having a concentration of 0.05 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard solution* with *Mobile phase.*

Related compounds stock solutions—Separately dissolve accurately weighed quantities of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Ci-

talopram Related Compound E RS in *Mobile phase* to obtain stock solutions having known concentrations of about 0.1 mg per mL of each compound.

Peak identification solution—Prepare a mixture containing about 0.001 mg per mL each of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Citalopram Related Compound E RS, using the *Standard stock solution* as the diluent.

Resolution solution—Dilute 0.5 mL of *Citalopram related compound C stock solution* and 25.0 mL of the *Standard stock solution* with *Mobile phase* to 50 mL to obtain a solution containing 0.01 mg per mL of citalopram related compound C and 0.25 mg per mL of citalopram hydrobromide.

Test solution—Transfer 10 Tablets into a 200-mL volumetric flask, add 25 mL of *Phosphate buffer,* and shake by mechanical means until disintegrated. Add about 100 mL of a mixture of methanol and water (50 : 50), mix, and sonicate for about 5 minutes. Allow to cool, dilute with a mixture of methanol and water (50 : 50) to volume, and mix thoroughly. Allow the excipients to settle. Dilute as necessary to obtain a final concentration of 0.5 mg per mL of citalopram. Pass a portion of this solution through a polytetrafluoroethylene (PTFE) membrane 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 239-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 45°. The flow rate is about 0.8 mL per minute. Inject the *Standard solution,* and record the peak responses as directed for *Procedure*: the citalopram peak shows no shoulders or excessive tailing; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 1.5; the capacity factor, k', is not less than 3.5; and the relative standard deviation of both the retention time and the response for replicate injections is not more than 5%. Inject the *Sensitivity solution* into the chromatograph, and verify that the signal-to-noise ratio is at least 3. Inject the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, R, between citalopram related compound C and citalopram is not less than 3. Inject the *Peak identification solution,* and record the responses as directed for *Procedure:* the four related compound peaks are baseline resolved from each other and the citalopram peak.

Procedure—Inject a volume (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 each Tablet by the formula:

$$100(r_i / r_S)(324.39/405.30)(C_S / C_T)(1/F)$$

in which r_i is the individual peak response for each citalopram related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; F is the relative response factor of each impurity relative to citalopram (free base); and C_S and C_T are the concentrations, in mg per mL, of citalopram hydrobromide in the *Standard solution* and the *Test solution,* respectively. The limits for the related compounds are listed in *Table 1.*

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Table 1

Related Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Citalopram related compound A	0.43	0.77	NMT* 0.1
Citalopram related compound B	0.60	0.98	NMT 0.25
Citalopram related compound C	0.83	0.69	NMT 0.25
Citalopram related compound E	1.32	0.91	NMT 0.1
Unknown	—	1.0	NMT 0.1 each
Total known and unknown	—	—	NMT 0.7

* NMT = not more than.

Assay—

Buffer—Transfer about 0.71 g of anhydrous dibasic sodium phosphate to a 500-mL volumetric flask, and add about 250 mL of water. Shake to dissolve, then dilute with water to volume.

Diluent—Prepare a solution of methanol and *Buffer* (80 : 20).

Internal standard solution—Dissolve an accurately weighed amount of USP Citalopram Related Compound F RS in *Diluent* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.25 mg per mL.

Mobile phase—Prepare a filtered and degassed solution of *Diluent* containing about 770 mg of dodecyltrimethylammonium bromide per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1.25 mg of citalopram hydrobromide per mL.

Standard preparation—Pipet 5.0 mL of the *Standard stock preparation* and 5.0 mL of the *Internal standard solution* into a 50-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer 10 Tablets to a 200-mL volumetric flask, add 25 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 100 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature, then dilute with *Diluent* to volume. Allow to stand until the residue settles before taking an aliquot for dilution. Transfer an accurately measured volume of the clear supernatant to a 50-mL volumetric flask to obtain a final concentration between 0.090 and 0.10 mg per mL of citalopram. Add 5.0 mL of *Internal standard solution,* dilute with *Diluent* to volume, and mix. Pass a portion through a filter (PTFE) having a 0.45-µm or finer porosity.

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 column temperature is maintained at 45°. Inject the *Stan-*

dard preparation, and record the peak responses as directed for *Procedure*: the relative retention times are about 1.36 for citalopram related compound F and 1.0 for citalopram; the resolution, *R,* between citalopram and citalopram related compound F is not less than 1.5; the column efficiency is not less than 2000 theoretical plates, calculated from the citalopram peak; and the relative standard deviation for replicate injections is not more than 1.5% for the citalopram peak.

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 citalopram peaks. Calculate the quantity, in percent of label claim, of citalopram per Tablet taken by the formula:

$$100(C_S / C_U)(324.39/405.30)(R_U / R_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard preparation* and Citalopram Hydrobromide in the *Assay preparation,* respectively; 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; and R_U and R_S are the ratio of peak responses of citalopram to the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

BRIEFING

Cloxacillin Benzathine, *USP 28* pages 524; **Cloxacillin Benzathine Intramammary Infusion,** *USP 28* page 525. It is proposed to replace the microbial-based *Assay* with an HPLC method. The procedure utilizes a 4.6-mm × 25-cm column that contains 10-µm packing L1. USP has received validation data indicating that LiChrosphere RP18 brand column is suitable for use in this *Assay.* Interested parties are encouraged to submit comments.

(VET: I. DeVeau) RTS—42440-1

Change to read:

Assay—~~Proceed as directed for cloxacillin under *Antibiotics—Microbial Assays* ⟨81⟩, using an accurately weighed quantity of Cloxacillin Benzathine dissolved quantitatively in methanol to yield a stock solution having a convenient concentration. Promptly dilute an accurately measured volume of this stock solution quantitatively and stepwise with *Buffer No. 1* to obtain a *Test Dilution* having a concentration assumed to be equal to the median dose level of the Standard.~~

■*0.1 M Phosphate buffer*—Dissolve 55.2 g of monobasic sodium phosphate in water, and dilute with water to 4 L.

Mobile phase—Combine 1000 mL of acetonitrile and 3000 mL of *0.1 M Phosphate buffer.* Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 4.6 ± 0.2. Pass through a 0.45-µm nylon filter, and degas. [NOTE—The retention time of cloxacillin is very sensitive to the acetonitrile content of the *Mobile phase*.]

Diluent—Transfer 13.8 g of monobasic sodium phosphate to a 2-L volumetric flask, mix, and dilute with water to volume. Combine 1800 mL of the resulting solution with 1200 mL of acetonitrile. Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 6.4.

Standard preparations—In duplicate, dissolve an accurately weighed quantity of USP Cloxacillin Sodium RS in *Diluent* to obtain solutions having known concentrations of about 112 µg per mL.

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Assay preparations—In duplicate, dissolve an accurately weighed quantity of Cloxacillin Benzathine in *Diluent* to obtain solutions having concentrations of about 128 µg per mL.

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 10-µm packing L1. The flow rate is about 1.5 mL per minute and the column temperature is 40°. Chromatograph the *Standard preparations,* and record the peak areas as directed for *Procedure:* the tailing factor is less than 2.0; the peak areas of the two *Standard preparations* agree within 98% to 102%; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparations* and the *Assay preparations* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{19}H_{18}ClN_3O_5S$ in each mg of Cloxacillin Benzathine taken by the formula:

$$P(C_S / C_U)(r_U / r_S)$$

in which P is the assigned potency in µg of cloxacillin per mg of USP Cloxacillin Sodium RS; C_S and C_U are the concentrations, in µg per mL, of cloxacillin sodium and cloxacillin benzathine in the *Standard preparations* and *Assay preparations,* respectively; and r_U and r_S are the average peak areas of the cloxacillin peaks obtained from the *Assay preparations* and the *Standard preparations,* respectively. ■2S (*USP29*)

BRIEFING

Cloxacillin Benzathine Intramammary Infusion, *USP 28* page 525—See briefing under *Cloxacillin Benzathine.*

(VET: I. DeVeau) RTS— 42440-2

Change to read:

Assay— ~~Proceed as directed for cloxacillin under *Antibiotics—Microbial Assays* ⟨81⟩, expelling the contents of 1 syringe of Intramammary Infusion into a high speed glass blender jar containing sufficient methanol to yield a volume of 500 mL, and blend for 3 to 5 minutes. Promptly dilute an accurately measured volume of this solution quantitatively and stepwise with *Buffer No. 1* to obtain a *Test Dilution* having a concentration assumed to be equal to the median dose level of the Standard.~~

■*0.1M Phosphate buffer, Mobile phase, Diluent, Standard preparations,* and *Chromatographic system*—Proceed as directed in the *Assay* under *Cloxacillin Benzathine*.

Assay preparations—In duplicate, quantitatively express the entire contents of a syringe of Cloxacillin Benzathine Intramammary Infusion into a 500-mL volumetric flask. Add about 300 mL of methanol, and stir for 45 minutes ± 1 minute. Dilute with methanol to volume, and stir for an additional 10 minutes ± 1 minute. Immediately transfer 45 mL of the resulting solution to a 50 mL polypropylene centrifuge tube, and centrifuge for 10 minutes. From the supernatant remove an aliquot, and dilute with a sufficient volume of *Diluent* to prepare a solution containing about 100 µg cloxacillin per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparations* and the *Assay preparations* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{19}H_{18}ClN_3O_5S$ in each syringe of Cloxacillin Benzathine Intramammary Infusion taken by the formula:

$$P(CD/1000)(r_U / r_S)$$

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in which *P* is the assigned potency, in µg of cloxacillin per mg, of USP Cloxacillin Sodium RS; *C* is the concentration, in µg per mL, of cloxacillin sodium in the *Standard preparations; D* is the dilution factor used in preparing the *Assay preparations;* and r_U and r_S are the average peak areas of the cloxacillin peaks obtained from the *Assay preparations* and the *Standard preparations,* respectively. ■2S (*USP29*)

BRIEFING

Cyclopropane, *USP 28* page 559—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-3

Change to read:

» Cyclopropane contains not less than 99.0 percent, ~~by volume,~~

■volume/volume, ■2S (*USP29*)
of C_3H_6.

Caution—Cyclopropane is highly flammable. Do not use where it may be ignited.

Change to read:

Packaging and storage ~~— Preserve in cylinders.~~

■Preserve in orange cylinders. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003). ■2S (*USP29*)
[NOTE—Maintain cylinders of Cyclopropane at 25 ± 2° for not less than 6 hours prior to withdrawing specimens for the tests and assay, and correct the results to 25° and 760 mm of mercury.]

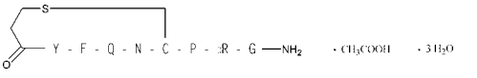
BRIEFING

Desmopressin Acetate; Desmopressin Injection; Desmopressin Nasal Spray Solution. Because there are no existing *USP* monographs for these articles, new monographs are being proposed. The test for *Amino acid content* involves acid hydrolysis and precolumn derivatization followed by HPLC using a 2.1-mm × 20-cm column that contains 5-µm packing L1. USP has received validation data indicating that an Agilent Hypersil AA-ODS model of column is suitable. The test for *Limit of acetic acid* uses a gas chromatographic method with flame-ionization detection and a 0.32-mm × 30-m fused silica capillary column coated with a 0.25-µm film of phase G35. Validation data indicate that a Phenomenex ZB-FFAP model of column is suitable. The HPLC procedures in the test for *Related compounds* and in the *Assay* utilize a 4.6-mm × 25-cm column that contains 5-µm packing L1. Validation data indicate that a LichroSphere C-18 model of column is suitable. Interested parties are encouraged to submit comments.

(BNT: I. DeVeau) RTS—38378-1; 40319-1; 42218-1

Add the following:

■Desmopressin Acetate



$C_{48}H_{68}N_{14}O_{14}S_2$

$C_{48}H_{68}N_{14}O_{14}S_2 \cdot xH_2O$

(anhydrous) 1129.27 [*62288-83-9*].

Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-, monoacetate (salt).

1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate (salt).

Trihydrate 1183.31 [*62357-86-2*].

» Desmopressin Acetate is a synthetic nonapeptide hormone having the property of antidiuresis. It is a synthetic analog of vasopressin. It contains

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not less than 95.0 percent and not more than 105.0 percent of desmopressin ($C_{46}H_{64}N_{14}O_{12}S_2$), calculated on the anhydrous, acetic acid-free basis.

Packaging and storage—Preserve in tight containers, preferably of Type I glass, protected from light. Store at a temperature not exceeding 25°, preferably between 2° and 8°.

Labeling—Label it to state the potency, in mg, of desmopressin.

USP Reference standards ⟨11⟩**—***USP Desmopressin Acetate RS.*

Identification—

A: *Ultraviolet Absorption*⟨197U⟩—

Solution: 1 mg in 5 mL.

Medium: 0.1 N sodium hydroxide.

B: *Mass spectral analysis—*

Diluent: a mixture of water and methanol (1 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Desmopressin Acetate RS in *Diluent* to obtain a solution having a known concentration of about 5 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Desmopressin Acetate in *Diluent* to obtain a solution having a known concentration of about 5 µg per mL. [NOTE—The final concentration of *Standard solution* and *Test solution* can be adjusted depending on the sensitivity of the mass spectrometer used in the testing.]

Mass spectrometric system (see *Mass Spectrometry* ⟨736⟩)—The LC/MS Spectrometer is equipped with an electrospray interface, positive ion mode, infusion system, and MS/MS capability.

Procedure—Separately infuse the *Standard solution* and the *Test solution* at about 5 µL per minute into the mass spectrometer. Obtain optimized MS and MS/MS spectra of the peak with mass-to-charge ratio 1069. For MS spectra, the major peak with mass-to-charge ratio of 1069 should be observed. For MS/MS spectra, product ions at mass-to-charge ratios of about 641, 742, and 995 are present.

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

Specific rotation ⟨781S⟩**:** between –72° and –82°, calculated on the anhydrous, acetic acid-free basis.

Test solution: 5 mg per mL, in diluted acetic acid.

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

Water, *Method I* ⟨921⟩**:** not more than 6.0%.

Amino acid content (see *Biotechnology-Derived Articles—Tests* ⟨1047⟩)**—**

Solution A—Prepare a solution having final concentrations of 20 mM sodium acetate, 0.2% (v/v) triethylamine, and 0.3% (v/v) tetrahydrofuran.

Solution B—Prepare a solution containing 20% (v/v) 100 mM sodium acetate, 40% (v/v) methanol, and 40% (v/v) 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⟩).

Borate buffer—Transfer 12.4 g of boric acid to a 500-mL volumetric flask, and suspend it in 300 mL of water. Add 100 mL of 1 N potassium hydroxide, and mix. Adjust with 1 N potassium hydroxide to a pH of 10.4, dilute with water to volume, and mix. Store in a closed plastic container.

Norvaline solution—Prepare a 4 mM solution of norvaline.

2% DTDPA solution—Transfer 2 g of dithiodipropionic acid to a 100-mL volumetric flask. Dissolve in and dilute with water to volume.

Sarcosine solution—Prepare a 4 mM solution of sarcosine.

0.1% Phenol—Prepare a solution containing 0.1% (w/v) phenol in 6 N hydrochloric acid.

OPA reagent—Prepare a solution containing 10 mg per mL each of *o*-phthalaldehyde and 3-mercaptopropionic acid in *Borate buffer.*

FMOC reagent—Prepare a solution containing 2.5 mg per mL of 9-fluorenylmethylchloroformate in acetonitrile.

Calibration solution—Prepare a mixture in which the final concentrations of amino acids are as follows: about 2.50 mM glycine; about 2.50 mM for the L-form of the amino acids lysine, histidine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, alanine, valine, methionine, isoleucine, leucine, tyrosine, and phenylalanine; and about 1.25 mM L-cystine. Transfer a 1-mL aliquot of this solution to a suitable vial, and add 5 µL each of *Norvaline solution* and *2% DTDPA solution.* Evaporate the aliquot to dryness, and add 300 µL of *0.1% Phenol.* Mix, and alternate between purging the head space of the vial with nitrogen gas and reducing the pressure to 2 mm of mercury for a total of two purge-vacuum cycles. Purge the sample with nitrogen gas one additional time, and reduce the pressure to 1.5 mm of mercury. Seal, and heat the sample at 110° for 24 hours. Open the vial, and evaporate to dryness. Dissolve the residue in 115 µL of *Borate buffer,* and add 5 µL of *Sarcosine solution.* Centrifuge for 2 minutes, and transfer the supernatant to a clean vial. Remove a 6-µL aliquot, and add 1 µL of *OPA reagent.* Mix, and add 1 µL of *FMOC reagent.* Mix, add 28 µL of water, and mix again.

Test solution—Dissolve an accurately weighed quantity of Desmopressin Acetate in water to obtain a solution having a known concentration of about 1.00 mg per mL. Add 5 µL each of *Norvaline solution* and *2% DTDPA solution* to a 1-mL aliquot, and prepare as directed in *Calibration solution,* beginning with "Bring the aliquot to dryness and add 300 µL of *0.1% Phenol.*"

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a thermoregulated autosampler, set at 4°, that is capable of adding and mixing derivatizing agents; a multi-wavelength detector set at 262 nm and 338 nm; and a 2.1-mm × 20-cm column that contains 5-µm packing L1. The flow rate is about 0.45 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–17	100→40	0→60	linear gradient
17–18.10	40→0	60→100	linear gradient
18.10–24	0	100	isocratic
24–25	0→100	100→0	linear gradient
25–35	100	0	re-equilibration

Process and inject the *Calibration solution* and *Test solution,* and record the peak responses for individual amino acid derivatives as directed for *Procedure*: the order of elution of the amino acid derivatives is aspartic acid, glutamic acid, serine, histidine, glycine, threonine, cysteine (reduced cystine), alanine, arginine, tyrosine, valine, methionine, norvaline, phenylalanine, isoleucine, leucine, lysine, and proline; the resolution, *R,* between the amino acid pairs histidine and glycine, alanine and arginine, and valine and methionine in the *Calibration solution* is not less than 1; and the relative standard deviation for triplicate injection of the *Calibration solution* is not greater than 15% for cysteine, lysine and proline, and not greater than 10% for all other amino acids. The peak area of the norvaline peak in the *Test solution* should be not less than 80% and not greater than 120% of that found in the *Calibration solution.*

Procedure—Using the autosampler, separately remove equal volumes (about 6 µL) of the *Calibration solution* and the *Test solution,* and to each add 1 µL of *OPA reagent.* Mix, and to each add 1 µL of *FMOC reagent.* Mix, add 28 µL of water to each, mix again, and inject the entire volume into the chromatograph. Record the area responses for the main peaks, and identify the amino acids. Using the *Calibration solution* as a standard, express the content of each amino acid in moles. With the content for arginine set to 1, calculate the relative proportions of the amino acids: aspartic acid, glutamic acid, proline, glycine, and phenylalanine are between 0.95 and 1.05; tyrosine is between 0.7 and 1.05; cysteine is between 0.30 and 1.05; lysine, isoleucine, and leucine are absent; and not more than traces of other amino acids are found.

Limit of acetic acid—

Internal standard solution—Transfer about 16 mL of hydrochloric acid into a 1000-mL volumetric flask containing about 500 mL of water, and mix. Add about 0.5 mL of propionic acid, accurately measured, dilute with acetonitrile to volume, and mix.

Standard solution—Transfer about 1.049 g of acetic acid, accurately measured, to a 100-mL volumetric flask. Dilute with *Internal standard solution* to volume, and mix. Transfer 2.5 mL of the resulting solution to a 50-mL volumetric flask. Dilute with *Internal standard solution* to volume, and mix.

Test solution—Dissolve about 5 mg of Desmopressin Acetate, accurately weighed, in 0.5 mL of *Internal standard solution,* and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused silica capillary column coated with a 0.25-µm film of phase G35. The carrier gas is helium, flowing at a rate of about 3 mL per minute, and the split flow ratio is 20 : 3. The column temperature is maintained at 120°, and the injector port and detector temperatures are maintained at 250°. Chromatograph six replicate injections of the *Standard solution,* and record the peak areas as directed for *Procedure:* the order of elution is acetic acid followed by propionic acid; the resolution, *R,* between acetic acid and propionic acid is not less than 5.0; the tailing factor for acetic acid is not more than 3.0; and the relative standard deviation of the peak area ratio of acetic acid to propionic acid is not more than 15%.

Procedure—Separately inject equal volumes (about 1.0 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the peak responses. Calculate the percentage of acetic acid in the portion of Desmopressin Acetate 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 acetic acid in the *Standard solution;* C_U is the concentration, in mg per mL, of desmopressin acetate in the *Test solution;* and R_U and R_S are the peak area ratios of acetic acid to the internal standard obtained from the *Test solution* and the *Standard solution,* respectively: not more than 8.0% is found.

Chromatographic purity—

Mobile phase and *System suitability solution*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Desmopressin Acetate RS in *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Desmopressin Acetate in *Mobile phase* to prepare a solution having a known concentration of about 200 µg per mL.

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, and the column is maintained at 30°. Chromatograph the *Standard solution* and *System suitability solution,* and record the peak areas as directed for *Procedure:* the desmopressin peak elutes before the oxytocin peak; the resolution, *R,* between desmopressin and oxytocin is not less than 1.5; the tailing factor is not greater than 2.0; and the relative standard deviation of the desmopressin peak area for replicate injections of the *Standard solution* is not greater than 5.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the response for each peak, except for the main desmopressin peak in the chromatogram of the *Test solution.* Calculate the percentage of each impurity in the portion of Desmopressin 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 USP Desmopressin Acetate RS, calculated on the anhydrous, acetic acid-free basis, in the *Standard solution;* C_U is the concentration, in mg per mL, of Desmopressin Acetate, calculated on the anhydrous, acetic acid-free basis, in the *Test solution;* r_i is the peak response of an individual impurity in the chromatogram obtained from the *Test solution;* and r_S is the desmopressin peak response obtained from the *Standard solution:* not more than 0.5% of any individual impurity is found, and the sum of all impurities is less than 1.5%.

Assay—

Buffer solution—Dissolve 3.4 g of monobasic potassium phosphate and 2.0 g of sodium 1-heptanesulfonic acid in 1000 mL of water. Adjust the pH to 4.50 ± 0.05 with phosphoric acid or sodium hydroxide, as needed. Pass through a 0.45-µm filter.

Mobile phase—Mix 780 mL of *Buffer solution* with 220 mL of acetonitrile, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—The retention time of desmopressin is very sensitive to the composition of the *Mobile phase.*]

Standard preparation—Dissolve an accurately weighed quantity of USP Desmopressin Acetate RS in *Mobile phase* to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Desmopressin Acetate in *Mobile phase* to prepare a solution having a known concentration of about 20 µg per mL.

System suitability solution—Dissolve about 1 mg of oxytocin, accurately weighed, in a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of the resulting solution and 5.0 mL of *Assay preparation* 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 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 30°. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation* and *System suitability solution,* and record the peak areas as directed for *Procedure:* the desmopressin peak elutes before the oxytocin peak; the resolution, *R,* between desmopressin and oxytocin is not less than

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1.5; the tailing factor is not greater than 2.0; and the relative standard deviation of the desmopressin peak area for replicate injections is not greater than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation,* both freshly prepared, into the chromatograph, record the chromatograms, and measure the desmopressin peak areas. Calculate the percentage of $C_{46}H_{64}N_{14}O_{12}S_2$ in the portion of Desmopressin Acetate 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 Desmopressin Acetate RS, calculated on the anhydrous, acetic acid-free basis, in the *Standard preparation;* C_U is the concentration, in mg per mL, of Desmopressin Acetate, calculated on anhydrous, acetic acid-free basis, in the *Assay preparation;* and r_U and r_S are the peak responses for desmopressin obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP29)*

BRIEFING

Desmopressin Injection—See briefing under *Desmopressin Acetate.*

(BNT: I. DeVeau) RTS—38378-2

Add the following:

■Desmopressin Injection

» Desmopressin Injection is a sterile solution of Desmopressin Acetate in a suitable diluent. It may contain suitable preservatives. It possesses, in each mL, an activity of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of desmopressin ($C_{46}H_{64}N_{14}O_{12}S_2$), calculated on the anhydrous, acetic acid-free basis.

Packaging and storage—Preserve in tight containers, protected from light. Store at a temperature between 2° and 8°.

Labeling—Label it to state the potency, in mg, of desmopressin.

USP Reference standards ⟨11⟩**—***USP Desmopressin Acetate RS. USP Endotoxin 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 desmopressin.

Sterility ⟨71⟩**—**It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

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pH ⟨791⟩**:** between 3.5 and 6.0.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

Other requirements—It meets the requirements for *Volume in Container* under *Injections* ⟨1⟩.

Assay—

Buffer solution—Dissolve 4.9 g of phosphoric acid, accurately weighed, in water. Dilute with water to 1000 mL. Adjust with triethylamine to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (83.5 : 16.5). Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution A—Transfer 9 g of sodium chloride, accurately weighed, to a 1000-mL flask, and dissolve in and dilute with water to volume. Adjust with hydrochloric acid to a pH between 3.5 and 5.0.

Solution B—Transfer 9 g of sodium chloride, accurately weighed, to a 1000-mL flask, dissolve in water, and add 5 g of chlorobutanol. Dilute with water to volume, and adjust with hydrochloric acid to a pH between 3.5 and 5.0.

Standard preparation—Dissolve an accurately weighed quantity of USP Desmopressin Acetate RS in water to obtain a solution having a known concentration of about 1 mg per mL. Dilute this solution with *Solution A* or *Solution B*, as directed for the *Assay preparation*, to obtain a solution with a concentration of desmopressin equivalent to that in the *Assay preparation*.

Assay preparation—For injections at concentrations of desmopressin between 4 µg per mL and 0.1 mg per mL, use undiluted Desmopressin Injection. For injections at concentrations exceeding 0.1 mg per mL and without preservatives, dilute 1000 µL of Desmopressin Injection, accurately measured, with 10 mL of *Solution A*. For injections at concentrations exceeding 0.1 mg per mL and containing preservatives, dilute 1000 µL of Desmopressin Injection, accurately measured, with 10 mL of *Solution B*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph about 50 µL of the *Standard preparation,* and record the peak responses as directed for *Procedure*: the tailing factor is not more than 1.4; 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*, both freshly prepared, into the chromatograph, and record the chromatograms for a total time of not less than 2.5 times the retention time of the desmopressin peak. Calculate the quantity of $C_{46}H_{64}N_{14}O_{12}S_2$, in mg, in the volume of *Injection* taken by the formula:

$$CD(r_U / r_S)$$

in which C is the concentration of desmopressin, in mg per mL, in the *Standard preparation; D* is the dilution factor used to prepare the *Assay preparation;* and r_U and r_S are the peak responses for desmopressin obtained from the *Assay preparation* and the *Standard preparation*, respectively.■2S (*USP29*)

In-Process Revision

BRIEFING

Desmopressin Nasal Spray Solution—See briefing under *Desmopressin Acetate*.

(BNT: I. DeVeau) RTS—38378-3

Add the following:

■Desmopressin Nasal Spray Solution

» Desmopressin Nasal Spray Solution is a solution of Desmopressin Acetate in a suitable diluent. It is supplied in a form suitable for nasal administration and contains suitable preservatives. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of desmopressin ($C_{46}H_{64}N_{14}O_{12}S_2$), calculated on the anhydrous, acetic acid-free basis.

Packaging and storage—Preserve in containers suitable for administering the contents by spraying into the nasal cavities in a controlled, individualized dosage. Protect from light, and store at a temperature between 2° and 8°.

Labeling—Label it to indicate that it is for intranasal administration only and to state the total number of discharges. Label it also to state that the dosage regulation is described in the package insert.

USP Reference standards ⟨11⟩**—***USP Desmopressin Acetate 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.*

Microbial limits ⟨61⟩**—**The total aerobic microbial count does not exceed 100 cfu per mL, the total combined molds and yeasts count does not exceed 10 cfu per mL, and it meets the requirements of the test for the absence of *Staphylococcus aureus and Pseudomonas aeruginosa.*

pH ⟨791⟩**:** between 3.5 and 6.0.

Uniformity of unit spray weight and total number of discharges per container—Select three Nasal Spray Solution units, and prime each spray pump as directed on the label, but not more than five times. Accurately weigh, by difference, 10 individual deliveries from each unit, weighing the first three discharges immediately after priming, and weighing four discharges from the middle of each unit, and three close to the end of each unit. Continue to fire until the unit is empty. For each unit, determine the total number of discharges, including the number of priming deliveries, and calculate the mean weight delivered per discharge: it contains not less than the number of discharges stated on the label; the mean weight delivered per discharge is within 10% of the labeled weight per discharge; and not fewer than nine tested discharges for each unit are between 85% and 125% of the labeled weight per discharge.

Assay—

Buffer solution, Mobile phase, Solution A, Solution B, and *Chromatographic system*—Prepare as directed in the *Assay* under *Desmopressin Injection*.

Assay preparation, Standard preparation, and *Procedure*—Proceed as directed for products containing preservatives in the *Assay* under *Desmopressin Injection.* ■2S (*USP29*)

In-Process Revision

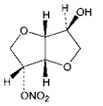
BRIEFING

Diluted Isosorbide Mononitrate, page 868 of *PF* 30(3) [May–June 2004]. On the basis of comments received, it is proposed to revise the lower limit of the *pH* range to 4.0.

(PA5: A. Wilk) RTS—41640-1

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 handling. It contains not less than ~~87.5 percent and not more than 92.5 percent (w/w)~~ 95.0 percent and not more than 105.0 percent of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

Caution—Exercise proper precautions in handling undiluted isosorbide mononitrate, which is a powerful explosive and can be exploded by percussion or excessive heat. Only exceedingly small amounts should be isolated.

Packaging and storage—Preserve in tight containers. Store between 20° and 30°.

USP Reference standards ⟨11⟩**—***USP Isosorbide RS. USP Diluted Isosorbide Dinitrate 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.*

Change to read:

pH ⟨791⟩**:** between ~~4.8~~ ■4.0■2S (*USP29*) 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 Ic* ⟨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.

In-Process Revision

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 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.*

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.

In-Process Revision

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 (*USP28*)

BRIEFING

Estradiol Transdermal System, page 1201 of *PF* 30(4) [July–Aug. 2004]. It is proposed to add a *Drug Release Test 2* for one generic product approved by FDA. The chromatographic procedure in this test was validated using a Nova-Pak C18 brand of L1 column.

(BPC: M. Marques) RTS—41485-1; 42016-2

Add the following:

■Estradiol Transdermal System

» Estradiol Transdermal System contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol ($C_{18}H_{24}O_2$).

Packaging and storage—Preserve in hermetic, light-resistant, unit-dose pouches.

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.

USP Reference standards ⟨11⟩—*USP Estradiol 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.*

Drug release ⟨724⟩**—**

TEST 1—

FOR PRODUCTS LABELED FOR DOSING EVERY 84 HOURS—

Medium: water; 900 mL, deaerated.

Apparatus 5: 50 rpm.

In-Process Revision

Times: 24, 48, and 96 hours.

Determine the amount of $C_{18}H_{24}O_2$ released by employing the following method.

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 solutions—Dissolve an accurately weighed quantity of USP Estradiol RS in dehydrated alcohol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 9 µg per mL. Dilute this solution with water to obtain additional solutions having known concentrations of about 0.9, 0.45, and 0.045 µg per mL.

Test solution—At each sampling time interval, withdraw a 10-mL aliquot of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a fluorometric detector, set at an excitation wavelength of 220 nm and an emission wavelength of 270 nm, and a 4.6-mm × 3-cm column that contains packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solutions,* and record the peak responses as directed for *Procedure:* the tailing factor is between 0.9 and 2.5; and the relative standard deviation for replicate injections of the 0.45 µg per mL *Standard solution* is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Plot the peak responses of the *Standard solutions* versus concentration, in µg per mL, of estradiol. From the graph so obtained, determine the amount, in µg per mL, of $C_{18}H_{24}O_2$ released, using the formulas that follow:

µg of estradiol released in the interval 0 to 24 hours:

$$\frac{900(A_1 - b)}{480m}$$

µg of estradiol released in the interval 24 to 48 hours:

$$\frac{900(A_1 - b) - 890(A_{n-1} - b)}{480m}$$

cumulative µg of estradiol released:

$$\left[\frac{900(A_n - b)}{20m}\right] + \frac{10}{20}\left[\sum_{x=1}^{n=1}\frac{(A_x - b)}{m}\right]$$

in which A_1 is the peak area of estradiol in the sample solution at the first release interval; A_n is the peak area of estradiol in the sample solution at the release interval *n; m* is the slope of the calibration curve; and *b* is the *y*-intercept of the calibration curve.

Tolerances—The amounts of $C_{18}H_{24}O_2$ released, as percentages of the labeled amount of the dose ~~absorbed in vivo~~ released to the skin at the times specified, conform to ~~*Acceptance Table 4.*~~ *Acceptance Table 1.*

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Time (hours)	Amount dissolved
24	between 2.4% and 26.4%
48	between 4.8% and 52.0%
96	between 10.0% and 85.0%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Medium: 0.005 M phosphate buffer, pH 5.5, containing 0.3% sodium lauryl sulfate; 500 mL.

Apparatus 5: 100 rpm. Use a 76-mm stainless steel disk assembly. Adhere the patch to the disk assembly using double-faced adhesive tape.

Times: 1, 4, 8, and 24 hours.

Determine the amount of estradiol ($C_{18}H_{24}O_2$) released by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed amount of USP Estradiol RS in acetone, and dilute quantitatively, and stepwise if necessary, with acetone to obtain a solution having a known concentration of about 800 µm per mL.

Standard working solution—Dilute the *Standard stock solution* with *Medium* to obtain a solution having a known concentration close to that expected in the solution under test, assuming 100% drug release.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.0-mm × 30-cm column that contains 4-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard working 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 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard working solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of estradiol released at each time point by the following formulas:

$$M_i = \frac{R_U \times C_S \times V_i}{R_S}$$

$$m_1 = M_1$$

$$m_2 = M_2 + M_1 \frac{V_a}{V_1}$$

$$m_3 = M_3 + M_2 \frac{V_a}{V_2} + M_1 \frac{V_a}{V_1}$$

$$m_4 = M_4 + M_3 \frac{V_a}{V_3} + M_2 \frac{V_a}{V_2} + M_1 \frac{V_a}{V_1}$$

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in which M_i is the amount, in mg, of estradiol released into the *Medium* at a given time interval; R_U is the peak response of estradiol in the sample solution, R_S is the peak response of estradiol in the *Working standard solution;* C_S is the concentration, in mg per mL, of estradiol in the *Standard working solution;* V_i is the corrected volume, in mL, of the *Medium* at a given time interval; m_i is the total amount, in mg, of estradiol released at a given time interval; m_1, m_2, m_3, and m_4 are the total amounts of estradiol, in mg, released from the patch at given time intervals; M_1, M_2, M_3, and M_4 are the amounts of estradiol, in mg, released into the *Medium* at given time intervals; V_a is the volume, in mL, of the aliquot taken from the dissolution vessel at each time point; and V_1, V_2, and V_3 are the volumes of the *Medium* at given time intervals.

Tolerances—The amounts of estradiol ($C_{18}H_{24}O_2$) released, as percentages of the labeled amount of the dose released to the skin, at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount released
1	between 15% and 40%
4	between 45% and 70%
8	between 70% and 90%
24	not less than 80%

Uniformity of dosage units ⟨905⟩**:** meets the requirements.

Alcohol content—

Diluent—Prepare a mixture of acetonitrile and water (1 : 1).

Internal standard solution—Pipet 4.0 mL of dehydrated methanol into a 100-mL volumetric flask. Dilute with water to volume, and mix.

Standard solution—Accurately weigh, by difference, about 1.6 mL of dehydrated alcohol into a tared 50-mL volumetric flask containing about 15 mL of water. Dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Pipet 25.0 mL of this solution into a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution,* dilute with water to volume, and mix.

Test solutions—Prepare as directed for *Assay preparations,* with the following changes. Pipet 25.0 mL of each solution into individual 50-mL volumetric flasks. Add 5.0 mL of *Internal standard solution,* dilute with water 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 glass column that contains support S2. The carrier gas is helium, flowing at a rate of 30 mL per minute. The column temperature is 100°. The injection port temperature and the detector temperature are maintained at 200°. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.4 for the internal standard and about 1.0 for alcohol; and the relative standard deviation for replicate injections, determined from the ratios of alcohol peak areas to those of the internal standard, is not more than 1.5%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and each of the *Test solutions* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount of alcohol, in mg, in each Transdermal System taken by the formula:

$$160C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of dehydrated alcohol in the *Standard solution;* and R_U and R_S are the ratios of the peak responses of alcohol to the internal standard obtained from the *Test solutions* and the *Standard so-*

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lution, respectively. Calculate the average amount of alcohol in the *Test solution* taken: between 80% and 120% of the labeled amount of C_2H_5OH is found.

Assay—

Diluent—Prepare a mixture of acetonitrile and water (1 : 1).

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Estradiol RS in *Diluent.* Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparations—Cut 10 Transdermal Systems into pieces, keeping the pieces from each system separate. Remove the protective liners, if any, from the strips, and discard. Transfer the pieces of each system into separate stoppered flasks of suitable size, and add an accurately measured volume of *Diluent* to each flask to obtain solutions having a concentration of about 0.1 mg of estradiol per mL. Shake by mechanical means for about 3 hours, and sonicate for 15 minutes.

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 packing L1. The column temperature is maintained at 35°. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is between 0.9 and 1.6; and the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparations* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of estradiol ($C_{18}H_{24}O_2$) in each Transdermal System taken by the formula:

$$VC(r_U / r_S)$$

in which V is the volume, in mL, of *Diluent* used to prepare the *Assay preparation; C* is the concentration, in mg per mL, of USP Estradiol 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. Calculate the average quantity, in mg, of estradiol in each Transdermal System. Use the individual assays to determine the *Uniformity of dosage units.* ■2S *(USP29)*

BRIEFING

Ethinyl Estradiol Tablets, *USP 28* page 789 and page 402 of *PF* 31(2) [Mar.–Apr. 2005] . It is proposed to increase the limit of any unknown impurity to the approved value of 0.5% in the test for *Related compounds.*

(PA1: C. Anthony) RTS—42590-1

Delete the following:

▲~~**Disintegration** ⟨701⟩: 30 minutes.~~ ▲*USP29*

Add the following:

▲**Dissolution** ⟨711⟩—[To come.] ▲*USP29*

Change to read:

Related compounds—

Solution A: acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50 : 50).

Solution B: 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 for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Diluent—Prepare a mixture of acetonitrile and water (50 : 50).

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—Quantitatively dilute portions of *Standard stock solution* with *Diluent* to obtain a solution containing about 0.12 µg per mL of USP Ethinyl Estradiol RS.

Test solution 1—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 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 210-nm 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 contains packing L11. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution	Flow rate (mL per min.)
0–20	100	0	equilibration/ isocratic	2
20–25	100→0	0→100	linear gradient	2.5
25–30	0	100	isocratic	3
30–32	0→100	100→0	linear gradient	2
32–35	100	0	re-equilibration	2

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0 for ethinyl estradiol; and the relative standard deviation for replicate injections is not more than 2.0%.

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 the relative retention time of 1.16; 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 the relative retention time of 1.2; 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 any other impurity taken by the formula:

$$100(r_U / r_S)$$

in which r_U 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. Not more than 0.5% of 17β-ethinyl estradiol is found; not more than 0.5% of estrone is found; not more than ~~0.1%~~ ★~~0.3%~~▲*USP29* ■0.5%■2S *(USP29)* of any unknown impurity is found; and not more than 2.0% of total impurities is found.

BRIEFING

Etodolac Extended-Release Tablets, page 3225 of the *First Supplement* to *USP 28.* It is proposed to add a *Labeling* section, to change the *Drug release* section title to *Dissolution,* and to add *Dissolution Test 2* and *Test 3* to the monograph. In the absence of any significant adverse comments, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of October 1, 2005.

(BPC: M. Marques) RTS—42027-1; 42515-1

Add the following:

•**Labeling**—When more than one *Dissolution Test* is provided, the labeling states the *Dissolution Test* used only if *Test 1* is not used.•5

Change to read:

~~**Drug release** ⟨724⟩—~~

•**Dissolution** ⟨711⟩—

TEST 1—•5

Medium: 0.05 M phosphate buffer, pH 7.4; 1000 mL.

Apparatus 2: 75 rpm, with USP sinker.

Times: 3, 6, 10, and 16 hours.

Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 279 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Etodolac RS in the same *Medium.* Use *Medium* as the blank.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to ~~*Acceptance Table 1*~~

•*Acceptance Table 2.*•5

Time (hours)	Amount dissolved
3	between 15% and 40%
6	between 35% and 70%
10	between 60% and 95%
16	not less than 80%

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.05 M phosphate buffer, pH 7.5; 1000 mL.

Apparatus 2: 100 rpm.

Times: 2, 4, 8, and 14 hours.

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Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by comparing the difference between the absorbances of the filtered portions of the solution under test determined at 278 nm and 245 nm with the difference between the absorbances of a Standard solution having a known concentration of USP Etodolac RS in the same *Medium* determined at the same wavelengths. Use *Medium* as the blank, and use a 0.05-cm silica cell.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 35%
4	between 30% and 55%
8	between 60% and 90%
14	not less than 85%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.05 M phosphate buffer, pH 6.8; 1000 mL.

Apparatus 2: 75 rpm.

Times: 2, 4, 8, and 14 hours.

Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm on portions of the solution under test passed through a 10-µm polyethylene filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Etodolac RS in the same *Medium*. Use *Medium* as the blank, and use a 0.05-cm silica cell.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 30%
4	between 30% and 50%
8	between 55% and 75%
14	not less than 80%

●[5]

BRIEFING

Flurbiprofen, *USP 28* page 865. Based on comments received, it is proposed to delete *Identification* test *C.*

(PA2: C. Anthony) RTS—42622-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 10 µg per mL.
Medium: 0.1 N sodium hydroxide.
Absorbance maximum at 247 nm is about 0.8.
~~**C:** Heat 0.5 mL of a saturated solution of chromium trioxide in sulfuric acid in a water bath for 5 minutes: the solution wets the sides of the tube readily and there is no greasiness. Add 2 or 3 mg of Flurbiprofen and heat in a water bath for 5 minutes: the solution does not wet the sides of the tube and does not pour easily.~~

■■2S (*USP29*)

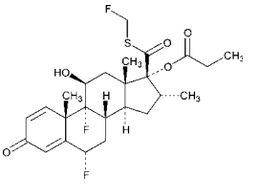
In-Process Revision

BRIEFING

Fluticasone Propionate, page 3233 of the *First Supplement.* On the basis of the comments received, it is proposed to revise the Definition to state the conditions under which the limits were established. It is also proposed to revise the limit in the test for *Content of acetone* to meet ICH guidelines. In addition, minor editorial revisions have been proposed.

(AER: K. Zaidi) RTS—41986-1; 42268-1

Change to read:



$C_{25}H_{31}F_3O_5S$ 500.57

Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy-, (6α,11β,16α,17α)-*S*-(fluoromethyl) ester.

~~*S*-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate~~

■*S*-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate■2S (*USP29*)
[*80474-14-2*].

Change to read:

» Fluticasone Propionate contains not less than 98.0 percent and not more than 100.5 percent of $C_{25}H_{31}F_3O_5S$, calculated on the anhydrous,

■solvent-free■2S (*USP29*)
basis.

Change to read:

Content of acetone—

Internal standard solution—Prepare a 0.05% (v/v) solution of tetrahydrofuran in dimethylformamide.

Standard solution—Prepare 0.05% (v/v) of acetone in *Internal standard solution*.

Test solution—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Internal standard solution* to obtain a solution having a known concentration of about 50 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 25-m column coated with a 2-µm film of phase G15. The carrier gas is nitrogen or helium, flowing at a rate of about 5.5 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at 60° for 3.5 minutes, then the temperature is increased at the rate of 30° per minute to 180°, and maintained at 180° for 3 minutes. The splitless injector temperature is maintained at 150°, and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections

■of the *Standard solution*■2S (*USP29*)
is not more than 5.0%.

Procedure—Separately inject equal volumes (about 0.1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the peak responses. Calculate the percentage of acetone (w/w) in the portion of Fluticasone Propionate taken by the formula:

$$0.05D/C(R_U/R_S),$$

in which D is the density of acetone at 20°; C is the concentration, in g per mL, of fluticasone propionate in the *Test solution;* and R_U and R_S are the ratios of the acetone peak response to the tetrahydrofuran peak response obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~1.0% (w/w)~~

■0.5% (w/w)■2S (*USP29*)
is found.

Change to read:

Assay—

0.01 M Monobasic ammonium phosphate buffer, pH 3.5—Dissolve ~~11.5 g~~

■1.15 g■2S (*USP29*)
of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer, pH 3.5,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve approximately ~~2.0 mg~~

■2.5 mg■2S (*USP29*)
of USP Fluticasone Propionate Resolution Mixture RS in 50 mL of *Mobile phase.*

Standard preparation—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-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 *Resolution solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 1.10 for fluticasone propionate related compound D and 1.0 for fluticasone propionate; and the resolution, *R,* between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections

■of the *Standard solution*■2S (*USP29*)
is not more than 2%.

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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 areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{31}F_3O_5S$ in the portion of Fluticasone Propionate taken by the formula:

$$CV(r_U / r_S),$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the *Standard preparation;* V is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Fluticasone Propionate Nasal Spray. Because there is no existing *USP* monograph for this dosage form, 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 the Spherisorb ODS1 brand of L1 column. The typical retention time for fluticasone propionate is about 13 minutes.

(AER: K. Zaidi) RTS—41571-1

Add the following:

■Fluticasone Propionate Nasal Spray

» Fluticasone Propionate Nasal Spray is a white opaque suspension of fluticasone propionate in water. It is supplied in a form suitable for nasal administration. It contains not less than 95 percent and not more than 115 percent of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

Packaging and storage—Preserve in tight, light-resistant containers, and store between 4° and 30°.

USP Reference standards ⟨11⟩**—***USP Fluticasone Propionate RS. USP Fluticasone Propionate Related Compound D RS. USP Fluticasone Propionate Related Compound F RS. USP Phenylethyl Alcohol RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—

Test specimen—Transfer about 30 g of Nasal Spray equally into two 50-mL centrifuge tubes. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. To one tube add 10 mL of methanol. Shake to disperse the residue, and transfer to the other tube. Shake this for 1 minute. Centrifuge at 3500 rpm for 10 minutes. Decant the supernatant into an agate mortar. Evaporate the methanol either by carefully blowing dry with compressed air or nitrogen, or by allowing the methanol to evaporate naturally. If using an air or nitrogen line, use a suitable in-line filter to avoid contamination. Allow the residue to dry overnight in a desiccator over silica gel.

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.*

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

pH ⟨791⟩**:** between 5.0 and 7.0.

Particle size—Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400 × magnification. Record the number of individual particles that are less than 5 µm in diameter: not less than 98% by number. Record the number of the individual particles that are greater than 5 µm in diameter but less than 15 µm in diameter: not more than 1.8% by number. Record the number of the individual particles that are greater than 15 µm in diameter: not more than 0.2% by number.

Foreign particulates—Shake the required number of bottles to ensure uniformity. Remove the pump system carefully to minimize contamination of the sample. Collect about 100 g of Nasal Spray, and pass it through a wetted 250-µm screen. Rinse each bottle with a portion of water equal to twice the volume of each bottle. Pass the rinse through the 250-µm screen. Visually observe the screen and filtrate for any foreign particulates. Also examine the screen under a microscope using transmitted light: free from any visible foreign particulates greater than 250 µm.

Delivered dose uniformity (within container)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, pH 3.5, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 4 µg per mL of each.

Standard solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 4 µg per mL.

Test solution—Wipe clean the pump, and record the weight of the bottle prior to actuation. Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations (1 dose) into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after the collection of two actuations. Weigh the bottle after sample collection. Discharge actuations 3 to 48 (50-spray pack) or 3 to 118 (120-spray pack) to waste. Wipe clean the bottle, and record the weight of the bottle. Collect the last two actuations (49 and 50 or 119 and 120) into a second 25-mL volumetric flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask, and record the weight of the bottle. Add 20 mL of the *Diluent* to each flask, and shake well for 10 minutes to disperse the suspension. Dilute with *Diluent* to volume, and mix thoroughly. Allow the flask to stand until the excipients have settled. Transfer a portion of the clear supernatant to an HPLC vial and inject. Repeat this procedure with 4 additional bottles.

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 quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Stan-*

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dard solution, respectively. The mean dose delivered from 10 doses is within 85% to 115% of label claim. Not more than 1 dose is outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim. Test an additional 10 bottles if 2 or 3 doses are outside ±20% of label claim. The mean dose delivered from 30 doses should be within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim.

Delivered dose uniformity (within batch)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, pH 3.5, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Standard solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Test solution—Wipe clean the pump, and record the weight of the bottle prior to actuation. Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after the collection of two actuations (1 dose). Repeat this procedure with 9 additional bottles.

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 quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The mean dose delivered from 10 doses is within 85% to 115% of label claim. Not more than 1 dose is outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim. Test an additional 20 bottles if 2 or 3 doses are outside ±20% of label claim. The mean dose delivered from the two actuations at the beginning of the 30 bottles (30 doses) is within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim.

Related compounds—

Solution A—Prepare a mixture of methanol and acetonitrile (77 : 23).

0.01 M Monobasic ammonium phosphate buffer—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.4 ±0.1, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *0.01 M Monobasic ammonium phosphate buffer* (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

Control solution—Prepare a solution in a mixture of water and *Diluent* (1 : 4) containing about 0.5 mg per mL of USP Phenylethyl Alcohol RS and 0.08 mg per mL of benzalkonium chloride.

System suitability solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS, USP Fluticasone Related Compound D RS, USP Fluticasone Propionate Related Compound F RS, and USP Phenylethyl Alcohol RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a

known concentration of about 100 µg per mL, 1.0 µg per mL, 1.0 µg per mL, and 500 µg per mL of each Reference Standard, respectively.

Test solution—Transfer accurately about 1.0 g of the Nasal Spray to a 5-mL volumetric flask, dissolve in and dilute with *Diluent* to volume. Shake the flask vigorously to dissolve. Pass through a 0.5-µm porosity filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *System suitability solution,* and measure the peak responses as directed for *Procedure:* the resolution, *R,* between fluticasone propionate related compound F and phenylethyl alcohol is not less than 1.5; the resolution, *R,* between fluticasone propionate related compound D and fluticasone propionate is not less than 2; and the relative retention times and limits are as provided in *Table 1.*

Procedure—Separately inject a volume (about 50 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Nasal Spray 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, excluding the peaks obtained from the *Control solution.*

Table 1

Compound	Approximate Relative Retention Time	Limit (%)
S-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioate/ *S*-Fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-3,6-dioxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate	0.7	0.3
Fluticasone propionate related compound D	1.1	0.3
6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio) carbonyl-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-dien-17α-yl ester	2.1	0.3
Unknown impurities	—	0.2
Total	—	1.5

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Content of phenylethyl alcohol—

Diluent, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Phenylethyl Alcohol RS in *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Use the *Assay preparation.*

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 per g, of phenylethyl alcohol in the portion of Nasal Spray taken by the formula:

$$50(C/W_U)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of the USP Phenylethyl Alcohol RS in the *Standard solution;* W_U is the weight, in g, of the Nasal Spray taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. For 50 sprays: not less than 1.75 mg per g and not more than 2.63 mg per g. For 120 sprays: not less than 1.88 mg per g and not more than 2.63 mg per g.

Content of benzalkonium chloride—

Citric acid buffer solution—Dissolve 50 g of citric acid in 200 mL of water. Adjust the solution with 2 N sodium hydroxide to a pH of 3.5 ± 0.05.

Docusate sodium titrant—Dissolve 0.22 g of docusate sodium in 100 mL of warm water, and dilute with water to make 1000 mL.

Eosin Y indicator—Dissolve about 25 mg of eosin Y in 50 mL of acetone. Add 450 mL of chloroform and 5.0 ± 0.5 g of citric acid. Shake thoroughly until no discoloration occurs. Filter the mixture to remove any undissolved citric acid. Store in an amber bottle.

Benzalkonium chloride standard stock solution—Use 50% (w/v) solution of benzalkonium chloride.[1]

Benzalkonium chloride standard solution—Transfer accurately about 0.4 g of *Benzalkonium chloride standard stock solution* to a 1000-mL volumetric flask. Dilute with water to volume, and mix. Sonicate for 5 minutes to dissolve.

Procedure—Pipet 10 mL of *Benzalkonium chloride standard solution* into a 250-mL glass stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Insert the stopper into the flask, and shake the mixture, releasing any build-up of pressure. Titrate with *Docusate sodium titrant* with vigorous shaking to a point when pink coloration is discharged from the chloroform layer. Perform a blank determination, substituting 10 mL of water for the *Benzalkonium chloride standard solution*, and make any necessary correction (see *Titrimetry* ⟨541⟩). Calculate the titer value of the *Docusate sodium titrant,* in µg of benzalkonium chloride per mL of *Docusate sodium titrant,* by the formula:

$$W_B/V_D$$

in which W_B is the weight, in µg, of benzalkonium chloride titrated; and V_D is the volume, in mL, of *Docusate sodium titrant.* Transfer accurately about 10 g of Nasal Spray into a 250-mL glass stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Repeat the procedure as given above for *Benzalkoni-*

[1] A suitable grade is available from Merck, Germany (www.merck.com).

um chloride standard solution. To clarify the endpoint, place the flask in an ultrasonic bath for 1 to 2 minutes to separate the chloroform layer from the aqueous phase. Perform a blank determination. Calculate the concentration of benzalkonium chloride, in µg per g, in the portion of Nasal Spray taken by the formula:

$$TV/W$$

in which T is the titer value of *Docusate sodium titrant; V* is the volume, in mL, of the *Docusate sodium titrant* used in the titration of the Nasal Spray; and W is the weight, in g, of the portion of Nasal Spray taken: not less than 160 µg per g and not more than 210 µg per g.

Assay—

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

0.01 M Monobasic ammonium phosphate buffer, pH 3.5—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer, pH 3.5,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Phenylethyl Alcohol RS, USP Fluticasone Propionate RS, and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 50 µg per mL, 10 µg per mL, and 1 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of the USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer accurately about 1.0 g of the Nasal Spray to a 50-mL volumetric flask, add about 40 mL of *Diluent,* and sonicate the flask for 10 minutes. Dilute with *Diluent* to volume, and shake. Allow to stand for about 10 minutes until the supernatant is a clear solution. Inject the clear supernatant into the chromatograph.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 4.6-mm × 25-cm column that contains 5-µm packing L1, and a programmable variable wavelength detector capable of monitoring at 210 nm and 239 nm. The flow rate is about 1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *Resolution solution* and the *Standard preparation,* record the peak areas at 210 nm for 5 minutes, and then change the wavelength to 239 nm and record the peak areas: the relative retention times are about 0.42 for phenylethyl alcohol, 1.0 for fluticasone propionate, and 1.10 for fluticasone propionate related compound D; the resolution, R, between fluticasone propionate and fluticasone propionate related compound D 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 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 fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Nasal Spray taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, 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 *(USP29)*

BRIEFING

Glycopyrrolate Tablets, *USP 28* page 914 and page 105 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to add a clarification to the *Identification* test.

(PA4: E. Gonikberg) RTS—42524-1

Change to read:

Identification—Blend a portion of finely powdered Tablets, equivalent to about 25 mg of glycopyrrolate, with 50 mL of water in a high-speed blender, and filter through very retentive filter paper

■or other suitable filter, to obtain a clear filtrate:■2S *(USP29)* the UV absorption spectrum of the filtrate exhibits maxima and minima at the same wavelengths as that of a solution of USP Glycopyrrolate RS (1 in 2000).

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

▲▲*USP29*
⟨711⟩—
Medium: water; 500 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure—

▲Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.▲*USP29*
Determine the amount of $C_{19}H_{28}BrNO_3$ dissolved, employing the procedure set forth in the *Assay,* making any necessary modifications.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{19}H_{28}BrNO_3$ is dissolved in 45 minutes:

▲the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

▲*USP29*

BRIEFING

Helium, *USP 28* page 939, page 3245 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 707 of *PF* 31(3) [May–June 2005]—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-4

Change to read:

» Helium contains not less than 99.0 percent, ~~by volume,~~

■volume/volume,■2S *(USP29)* of He.

In-Process Revision

Change to read:

Packaging and storage~~— Preserve in cylinders.~~

■Preserve in brown cylinders. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)

NOTE—Reduce the container pressure by means of a regulator. Measure the gases with a gas volume meter downstream from the detector tube in order to minimize contamination or change of the specimens.

BRIEFING

Hyoscyamine Sulfate, *USP 28* page 986. It is proposed to make the following changes:

1. Replace the current tests for *Melting temperature, Other alkaloids,* and *Readily carbonizable substances* with a more specific test for *Chromatographic purity*. The *Melting temperature* information is being placed under *Description and Solubility.*
2. Replace the current *Identification* test *B* with the HPLC retention time agreement of the major peak in the chromatograms of the *Test solution* and the *Standard solution*.
3. Replace the nonselective test for *Loss on drying* with the selective *Water* determination by Karl Fischer titration.
4. Change the limits in the test for *Residue on ignition* from 0.2% to 0.1%, to reflect the quality of currently marketed material.
5. Change the weight of the sample under the *Assay* from 1.0 g to 0.5 g.

The stability-indicating liquid chromatographic procedure in the test for *Chromatographic purity* is based on analyses performed with the Aquasil C18 brand of L1 column. The typical retention time for hyoscyamine is about 9.8 minutes.

(PA4: E. Gonikberg) RTS—42082-1; 42082-2

Change to read:

USP Reference standards ⟨11⟩—*USP Hyoscyamine Sulfate RS.*

■*USP Hyoscyamine Related Compound A RS.*■2S (*USP29*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: ~~To about 1 mL of a solution (1 in 20) add gold chloride TS, dropwise with shaking, until a definite precipitate separates. Add a small amount of 3 N hydrochloric acid, dissolve the precipitate with the aid of heat, and allow the solution to cool: lustrous golden yellow scales are formed (*distinction from atropine and scopolamine*).~~

■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.*■2S (*USP29*)

C: A solution (1 in 20) responds to the tests for *Sulfate* ⟨191⟩.

Delete the following:

■~~**Melting temperature** ⟨741⟩: not less than 200°.~~■2S (*USP29*)

Delete the following:

■~~**Loss on drying** ⟨731⟩—Dry it in vacuum at 105° for 16 hours: it loses between 2.0% and 5.5% of its weight.~~■2S (*USP29*)

Add the following:

■**Water,** *Method Ia* ⟨921⟩: between 2.0% and 5.5%.■2S (*USP29*)

Change to read:

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

■0.1%.■2S (*USP29*)

Delete the following:

■~~**Other alkaloids**—Dissolve 250 mg in 1 mL of 0.1 N hydrochloric acid, and dilute with water to 15 mL. To 5 mL of the solution add a few drops of platinic chloride TS: no precipitate is formed. To another 5 mL portion add 2 mL of 6 N ammonium hydroxide: the mixture may develop a slight opalescence, but no turbidity or precipitate is formed immediately.~~■2S (*USP29*)

Delete the following:

■~~**Readily carbonizable substances** ⟨271⟩—Dissolve 200 mg in 5 mL of sulfuric acid TS: the solution has no more color than *Matching Fluid A.*~~■2S (*USP29*)

In-Process Revision

Add the following:

■**Chromatographic purity**—

Buffer solution—Dissolve 7.0 g of monobasic potassium phosphate in 1000 mL of water, adjust with 0.05 M phosphoric acid to a pH of 3.3, and mix.

Solution A—Dissolve 3.5 g of sodium dodecyl sulfate in 606 mL of *Buffer solution,* add 320 mL of acetonitrile, 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⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Hyoscyamine Sulfate RS in *Solution A* to obtain a solution having a known concentration of about 1.2 mg of hyoscyamine sulfate per mL.

Standard solution—Dilute a portion of the *Standard stock solution* with *Solution A* to obtain a solution having a known concentration of about 0.24 mg of hyoscyamine sulfate per mL.

Diluted standard solution—Dilute the *Standard solution* with *Solution A* to obtain a solution having a known concentration of about 0.24 µg of hyoscyamine sulfate per mL.

System suitability solution—Prepare a solution of USP Hyoscyamine Related Compound A RS in *Solution A* having a concentration of about 2.4 µg per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, add 10 mL of the *Standard stock solution,* and dilute with *Solution A* to volume.

Test solution—Transfer about 60 mg of Hyoscyamine Sulfate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix. Transfer 10 mL of this solution to a 50-mL volumetric flask, and dilute with *Solution A* to volume. This solution contains about 0.24 mg of hyoscyamine sulfate per mL.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 10-cm column that contains 3-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
0–2	95	5	isocratic
2–20	95→70	5→30	linear gradient
20–20.1	70→95	30→5	linear gradient
20.1–25	95	5	re-equilibration

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 1.0%. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the resolution between hyoscyamine related compound A and hyoscyamine peaks is greater than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Diluted standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses of the major peaks. Calculate the percentage of each impurity in the portion of Hyoscyamine sulfate taken by the formula:

$$0.1(C_S / C_T)\ (r_i / r_S)$$

in which C_S is the concentration, in µg per mL, of hyoscyamine sulfate in the *Diluted standard solution;* C_T is the con-

centration, in mg per mL, of hyoscyamine sulfate in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the hyoscyamine peak response obtained from the *Diluted standard solution*. 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 is found.

Table 1

Name	Relative Retention Time	Limit (%)
DL-Tropic acid	0.2	0.2
7-Hydroxyhyoscyamine	0.67	0.2
6-Hydroxyhyoscyamine	0.72	0.2
Scopolamine	0.8	0.2
Norhyoscyamine (Hyoscyamine related compound A)	0.9	0.3
Apoatropine	1.1	0.2
Littorine	1.8	0.2

■2S (*USP29*)

Change to read:

Assay—Dissolve about ~~1 g~~ ■0.5 g■2S (*USP29*) of Hyoscyamine Sulfate, accurately weighed, in 50 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. Each mL of 0.1 N perchloric acid is equivalent to 67.68 mg of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4$.

BRIEFING

Irbesartan Tablets, page 1035 of *PF* 29(4) [July–Aug. 2003]. It is proposed to make modifications in the *Dissolution* test so that the test will be in accordance with the dissolution conditions approved by FDA.

(BPC: M. Marques) RTS—40548-10; 41088-1

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~~ 0.1 N hydrochloric acid; ~~900 mL~~ 1000 mL.

Apparatus 2: 50 rpm.

Time: ~~45 minutes~~ 20 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~~ 244 nm on ~~filtered portions of the solution under test,~~ portions of the solution

In-Process Revision

under test passed through a 0.45-µm filter of acrylic copolymer on a nylon support,[1] suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Irbesartan RS in the same *Medium*. Calculate the amount of $C_{25}H_{28}N_6O$ dissolved, in percentage, by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the concentration of the Standard solution; 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the label claim, in mg, of irbesartan.

Tolerances—Not less than ~~75%~~ 80% *(Q)* of the labeled amount of $C_{25}H_{28}N_6O$ is dissolved in ~~45 minutes~~ 20 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.

Assay—

~~*Diluent, Triethylamine solution, and Mobile phase*—Proceed as directed in the *Assay* under *Irbesartan.*~~

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 0.1 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 (see *Chromatography* ⟨621⟩)—~~Proceed as directed in the *Assay* under *Irbesartan.*~~ 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 preparation,* and record the peak responses as directed for *Procedure:* the col-

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[1] A suitable filter is Acrodisc, manufactured by Gelman Sciences and distributed by Pall Corp. (www.pall.com).

umn 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.■2S (*USP29*)

BRIEFING

Isosorbide Mononitrate Extended-Release Tablets, page 871 of *PF* 30(3) [May–June 2004]. It is proposed to add a *Dissolution* test to this new monograph. The liquid chromatographic procedures in the *Dissolution* test were validated using a Zorbax ODS brand of L1 packing. The retention time of isosorbide is about 5.5 minutes.

(BPC: M. Marques) RTS—42534-1

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.*

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.]~~

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm. The Tablets are placed in a metal helix, prepared by winding 10 inches of a 0.8-mm stainless steel wire around a 9/32-inch shaft and pulling the coils to form a helix 1 inch long.

Times: 1, 2, 4, 8, and 12 hours.

In-Process Revision

Determine the amount of isosorbide mononitrate dissolved by employing the following method.

Standard solution—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate RS in *Medium*, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.06 mg per mL.

Test solution—Use portions of the solution under test passed through a 0.45-µm nylon filter, discarding the first 4 to 6 mL of the filtrate.

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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 *Standard solution,* and record the chromatogram 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 solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Determine the amount, in mg, of isosorbide mononitrate dissolved *(AD)* at each interval by the formula:

$$\frac{r_U \times C_S \times V}{r_S}$$

in which r_U and r_S are the peak responses for the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* and V is the volume, in mL, of *Medium* in the vessel at each time point.

Calculate the amount, in mg, of isosorbide mononitrate removed *(AR)* by sampling at the previous time points by the formula:

$$\sum AD \times \frac{V_S}{V}$$

in which AD is the amount, in mg, of isosorbide mononitrate dissolved at each time point; V_S is the volume, in mL, of the sample taken; and V is the volume, in mL, of *Medium* in the vessel at each time point.

Calculate the percentage of isosorbide mononitrate dissolved at each time point by the formula:

$$\frac{(AD + AR) \times 100}{LC}$$

in which AD is the amount, in mg, of isosorbide mononitrate dissolved at a given time point; AR is the amount, in mg, of isosorbide mononitrate removed at the previous time point; 100 is the conversion factor to percentage; and LC is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 12% and 32%
2	between 23% and 43%
4	between 39% and 59%
8	between 65% and 85%
12	not less than 80%

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content Uniformity.* Proceed as directed in the *Assay,* except to use 1 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.*

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.

In-Process Revision

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*~~ *Resolution 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*~~ *Standard 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 percentage of each other impurity (other than isosorbide

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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)~~ 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 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 (*USP29*)

BRIEFING

Lidocaine and Prilocaine Cream. Because there is no existing *USP* monograph for this dosage form, a new monograph is proposed. The proposed liquid chromatographic procedures for *Related compounds* and the *Assay* are based on a Luna C18 brand of L1 column. The retention times for prilocaine and lidocaine are approximately 10 minutes and 20 minutes, respectively.

(PA1: K. Russo; AMB: R. Tirumalai; NL: L. Paul; PSD: C. Okeke) RTS—42219-1; 42219-2

Add the following:

■Lidocaine and Prilocaine Cream

» Lidocaine and Prilocaine Cream contains not less than 95.0 percent and not more than 105.0 percent of the labeled amounts of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$).

Packaging and storage—Preserve in collapsible tubes or in tight containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Lidocaine RS. USP Prilocaine Hydrochloride RS. USP Prilocaine Related Compound B 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.*

Microbial limits ⟨61⟩**—**It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

pH ⟨791⟩**:** between 9.3 and 9.9, in a solution (1 in 10).

Related compounds—

Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.002 mg per mL of each compound. Immediately store this solution at or below 10°.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are listed in *Table 1;* and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard solution* a minimum of six times, 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

peak responses. Calculate the percentage of each related compound in the portion of the Cream taken by the formula:

$$100C(r_U / r_S)(V / W)(100/L)(1/F)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard solution;* r_U and r_S are the individual peak responses for either lidocaine or prilocaine obtained from the *Test solution* and the *Standard solution,* respectively; V is the volume, in mL, of the *Test solution;* W is the weight, in mg, of the Cream taken to prepare the *Test solution;* L is the individual label claim, in percent, for lidocaine and prilocaine; F is the relative response factor for each related compound as listed in *Table 1;* and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectively (these are used only for calculation involving prilocaine related compounds). The percentages of lidocaine related compounds and prilocaine related compounds are calculated using the concentration and peak response from USP Lidocaine RS and USP Prilocaine Hydrochloride RS, respectively. The designation of whether an impurity is a lidocaine related compound or prilocaine related compound is specified in *Table 1*. The percent of any individual unknown related compound is determined using the concentration and peak response from USP Prilocaine Hydrochloride RS in the *Standard solution*.

Table 1

Related Compound	Relative Retention Time[1]	Relative Response Factor (*F*)	Limit
o-Toluidine	0.38	0.44 (P)[2]	not more than 0.1%
n-Chloroacetyl-2,6-xylidine	0.54	1.0 (L)[3]	not more than 0.1%
2,6-Dimethylaniline	0.67	0.30 (L)[3]	not more than 0.1%
(*RS*)-2-Chloro-*N*-(2-methylphenylenyl)propanamide	0.83	1.0 (P)[2]	not more than 0.2%
Prilocaine	1.00	—	—
Prilocaine related compound B	1.09	0.83 (P)[2]	not more than 0.2%
2-Diethylaminoaceto-2,4-xylidine	1.33	1.24 (L)[3]	not more than 0.1%
Lidocaine	2.14	—	—
n-Dichloroacetyl-2,6-xylidine	2.98	0.46 (L)[3]	not more than 0.1%
Any other individual related compounds	—	1.0 (P)[2]	not more than 0.2%
Total related compounds	—	—	not more than 1.0%

[1] relative to the prilocaine peak
[2] P designates a prilocaine related compound
[3] L designates a lidocaine related compound

Assay—

Solution A—Dissolve about 2.73 g of monobasic potassium phosphate in 630 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

Solution B—Dissolve about 2.73 g of monobasic potassium phosphate in 900 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

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

Standard preparation—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A*, and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.2 mg per mL of each compound. Immediately store this solution at or below 10°.

System suitability solution—Dissolve an accurately weighed quantity of USP Prilocaine Related Compound B RS in the *Standard preparation,* and dilute quantitatively, and stepwise if necessary, with the *Standard preparation,* to obtain a solution having a known concentration of about 0.08 mg per mL of prilocaine related compound B.

Assay preparation—Transfer a portion of the Cream, equivalent to about 20 mg each of lidocaine and prilocaine, accurately weighed, to a 100-mL volumetric flask. Add 5 mL of 5 N sodium hydroxide to disperse the Cream, and mix. Add 5 mL of 5 N hydrochloric acid, and dilute with *Solution A* to volume, and mix. Pass a portion through a nylon filter having a 0.2-µm porosity or finer, discarding the first 1 mL, and use the filtrate. Immediately store this solution at or below 10°.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 232-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. The samples are maintained at or below 10°. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	67	33	equilibration
0–11.0	67	33	isocratic
11.0–22.0	67→100	33→0	linear gradient
22.0–32.0	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are listed in the table; and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard preparation* a minimum of five times, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates, based on the prilocaine peak; the tailing factor is not more than 1.5, based on the prilocaine peak; 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 lidocaine and prilocaine

peaks. Calculate the percent of label claim of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$) in the portion of Cream taken by the formula:

$$100C(r_U / r_S)(V/W)(100/L)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard preparation;* r_U and r_S are either the individual peak responses of lidocaine or prilocaine obtained from the *Assay preparation* and the *Standard preparation,* respectively; V is the volume, in mL, of the *Assay preparation;* W is the weight, in mg, of the Cream taken to prepare the *Assay preparation;* L is the individual label claim, in percent, for either lidocaine or prilocaine; and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectivley (these are used only for calculating the percent of prilocaine in the Cream).■2S (*USP29*)

BRIEFING

Lisinopril Tablets, *USP 28* page 1140 and page 121 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to add the option of carrying out the *Dissolution* test in unit samples.

(BPC: M. Marques) RTS—41893-2

In-Process Revision

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

■■2S (*USP29*)
⟨711⟩—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.
Determine the amount of lisinopril dissolved using the following method.
Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*
~~*Procedure*~~

■PROCEDURE FOR POOLED SAMPLE—■2S (*USP29*)

■Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.■2S (*USP29*) Inject a volume of ~~a filtered portion of the solution under test~~ ■the pooled sample■2S (*USP29*) into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the same medium and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ in the Tablets is dissolved in 30 minutes:

■the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

PROCEDURE FOR UNIT SAMPLE—Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Inject a volume 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 $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the *Medium* and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ is dissolved in 30 minutes.■2S (*USP29*)

BRIEFING

Magnesium Oxide, *USP 28* page 1172 and page 1047 of *PF* 29(4) [July–Aug. 2003]. Comments were received that the proposed density specifications, as well as the differentiation between Light and Heavy Magnesium Oxide, are of historic importance only and do not represent the pharmaceutical grade material available on the market. It is proposed to delete the density specifications from the test for *Bulk density.* The *Labeling* section is revised to delete the references to the Light and Heavy Magnesium Oxide and to indicate the bulk density of the material.

(PA4: E. Gonikberg) RTS—41017-1

Change to read:

Labeling—~~Label it to indicate whether it is Light Magnesium Oxide or Heavy Magnesium Oxide.~~

■Label it to indicate its bulk density. The indicated density may be in the form of a range.■2S (*USP29*)

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~~ the bulk density of Magnesium Oxide.■2S (*USP29*)

BRIEFING

Mefloquine Hydrochloride, page 3253 of the *First Supplement* and page 422 of *PF* 31(2) [Mar.–Apr. 2005]. An editorial change is proposed in the test for *Related compounds* to clarify the preparation of the *Mobile phase.*

(PA7b: B. Davani) RTS—42631-1

Change to read:

Related compounds—

Mobile phase—Dissolve 1 g of tetraheptylammonium bromide in a

■1-L■2S (*USP29*)
mixture of a 1.5 g per L solution of sodium hydrogen sulfate, acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 4 mg of USP Mefloquine Hydrochloride RS and 4 mg of USP Mefloquine Related Compound A RS to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. [NOTE—Mefloquine related compound A is *threo*-mefloquine.] 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~~

▲0.7▲*USP29*
for ~~quinidine~~

▲mefloquine related compound A▲*USP29*
and 1.0 for mefloquine; the resolution, *R,* between mefloquine related compound A and mefloquine is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Equilibrate the column with *Mobile phase* at a flow rate of about 0.8 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 the chromatogram of the *Diluted test solution.* The response of the mefloquine related compound A 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 the *Test solution* is not greater than five times the response of the main peak in the chromatogram of the *Diluted test solution* (0.5%).

BRIEFING

Metformin Hydrochloride, *USP 28* page 1231 and page 62 of *PF* 31(1) [Jan.–Feb. 2005]; **Metformin Hydrochloride Tablets,** page 3255 of the *First Supplement.* In the *Procedure* section of the test for *Related compounds,* it is proposed to add formulas for calculation of the percentage of impurities. It is also proposed to revise the preparation of the *Resolution solution.*

(PA4: E. Gonikberg) RTS—42526-1

Add the following:

▲**Packaging and storage**—Preserve in well-closed containers. ~~Store at 25°, excursions permitted between 15° and 30°.~~ Store at room temperature.▲*USP29*

Change to read:

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.~~

■Prepare a solution in water containing about 0.25 mg of metformin hydrochloride and about 0.1 mg of melamine per mL.■2S *(USP29)*
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 area of the corresponding peak in the chromatogram of the *Standard solution:*~~

■Calculate the percentage of metformin related compound A in the portion of Metformin Hydrochloride taken by the formula:

$$10C/W(r_U/r_S)$$

in which C is the concentration, in µg per mL, of the USP Metformin Related Compound A RS in the *Standard solution; W* is the weight, in mg, of Metformin Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the metformin related compound A peak responses obtained from the *Test solution* and the *Standard solution,* respectively:■2S *(USP29)*
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:*~~

■Calculate the percentage of any other impurity in the portion of Metformin Hydrochloride taken by the formula:

$$0.1(r_i/r_S)$$

in which r_i is the peak response for an individual impurity obtained from the *Test solution;* and r_S is the metformin peak response obtained from the *Diluted test solution:*■2S *(USP29)*
not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

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BRIEFING

Metformin Hydrochloride Tablets, page 3255 of the *First Supplement*—See briefing under *Metformin Hydrochloride.* On the basis of comments received, in *Identification* test *A* it is also proposed to increase the drying time of the residue from 1 hour to 2 hours to ensure the removal of the dehydrated alcohol used to prepare the *Test specimen*.

(PA4: E. Gonikberg) RTS—42525-1; 42526-2

Change to read:

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.~~

■2 hours.■2S (*USP29*)

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-naphthol 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⟩.

Change to read:

Related compounds—

Mobile phase, Resolution 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.

Diluted test solution—Proceed as directed for *Metformin Hydrochloride,* except to use the *Test solution* prepared as described herein.

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 six times the area of the major peak in the chromatogram of the *Diluted test solution.*~~

■Calculate the percentage of each impurity in the portion of Metformin Hydrochloride Tablets taken by the formula:

$$0.1(r_i / r_S)$$

in which r_i is the peak response for an individual impurity obtained from the *Test solution;* and r_S is the metformin peak response obtained from the *Diluted test solution:*■2S (*USP29*) not more than 0.1% of any impurity is found; and not more than 0.6% of total impurities is found.

BRIEFING

Naphazoline Hydrochloride, *USP 28* page 1333. It is proposed to replace the current titration *Assay* procedure with an HPLC method. In addition, the upper *Assay* specification is being revised to reflect the change in the analytical technique. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the LiChroCART 125-4 brand of L1 column. The typical retention time for naphazoline hydrochloride is about 1.8 minutes.

(PA6: L. Evans) RTS—42447-1

Change to read:

» Naphazoline Hydrochloride contains not less than 98.0 percent and not more than ~~100.5~~

■102.0■2S (*USP29*) percent of $C_{14}H_{14}N_2 \cdot HCl$, calculated on the dried basis.

Change to read:

Assay— ~~Dissolve about 300 mg of Naphazoline Hydrochloride, accurately weighed, in 50 mL of glacial acetic acid, and add 10 mL of mercuric acetate TS and 1 drop of crystal violet TS. Titrate (see *Titrimetry* ⟨541⟩) with 0.1 N perchloric acid VS to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 24.67 mg of $C_{14}H_{14}N_2 \cdot HCl$.~~

In-Process Revision

■*Buffer*—In a 1000-mL volume flask, dissolve 3.0 g of monobasic potassium phosphate, accurately weighed, in 800 mL of water. Add 3.0 mL of triethylamine, adjust with phosphoric acid to a pH of 3.0, dilute with water to volume, and mix.

Mobile phase—Prepare a filterd and degassed solution of *Buffer* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Naphazoline Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, to obtain a concentration of 0.05 mg per mL.

Assay preparation—Transfer about 200 mg of Naphazoline Hydrochloride, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with water to volume. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

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. 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 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* 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 $C_{14}H_{14}N_2 \cdot HCl$ in the portion of Naphazoline Hydrochloride taken by the formula:

$$4000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Naphazoline 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 (*USP29*)

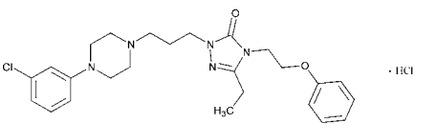
BRIEFING

Nefazodone Hydrochloride. Because there is no existing *USP* monograph for this active drug substance, a new monograph is proposed. The proposed liquid chromatographic tests in the *Assay* and in the test for *Related compounds* are based on analyses performed with the Waters Symmetry C18 brand of L1 column. Typical retention time for nefazodone hydrochloride is about 12 minutes.

(PA3: R. Ravichandran; NL: L. Paul; PSD: C. Okeke) RTS—41818-1; 41818-3; 41818-4

Add the following:

■Nefazodone Hydrochloride



$C_{25}H_{32}ClN_5O_2 \cdot HCl$ 506.47

3*H*-1,2,4-Triazol-3-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl)]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-, monohydrochloride.

1-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-3-ethyl-4-(2-phenoxyethyl)-Δ^2-1,2,4-triazolin-5-one monohydrochloride [*82752-99-6*].

In-Process Revision

» Nefazodone Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{32}ClN_5O_2 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers. Store at a temperature between 15° and 30°.

USP Reference standards ⟨11⟩**—***USP Nefazodone Hydrochloride RS. USP Nefazodone Related Compound A RS. USP Nefazodone Related Compound B RS.*

Completeness of solution ⟨641⟩**—**A 25 mg per mL solution in methanol meets the requirements.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: A solution of 10 mg per mL meets the requirements of the test for *Chloride* ⟨191⟩.

Loss on drying ⟨731⟩**—**Dry it in vacuum at 105° 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⟩**:** 0.001%.

Related compounds—

Diluent—Prepare a solution of water and acetonitrile (50 : 50).

Solution A—Dissolve 0.77 g of ammonium acetate in about 950 mL of water. Adjust with triethylamine to a pH of 7.10 ± 0.05. Dilute with water to 1 L. Filter and degas.

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 amount of USP Nefazodone Hydrochloride RS in *Diluent* to obtain a solution containing 0.1 mg per mL of nefazodone hydrochloride.

Nefazodone related compound A stock solution and *Nefazodone related compound B stock solution*—Transfer about 20 mg of each USP Nefazodone Related Compound A RS and USP Nefazodone Related Compound B RS, accurately weighed, into separate 200-mL volumetric flasks. Dissolve in and dilute with *Diluent* to volume.

Resolution solution— Pipet 5.0 mL of *Nefazodone related compound A stock solution* and 5.0 mL of *Nefazodone related compound B stock solution* into a 100-mL volumetric flask. Dilute with *Standard stock solution* to volume, and mix. This solution contains about 90 µg per mL of nefazodone hydrochloride, and about 5 µg per mL each of nefazodone related compound A and B.

Standard solution—Pipet 2.0 mL each of the *Standard stock solution, Nefazodone related compound A stock solution,* and *Nefazodone related compound B stock solution* into a 200-mL volumetric flask. Dilute with *Diluent* to volume, and mix well to obtain a final concentration of 1 µg per mL each of nefazodone hydrochloride, nefazodone related compound A, and nefazodone related compound B.

Test solution—Transfer about 100 mg of Nefazodone Hydrochloride, 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 250-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.7 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	equilbration
0–10	50→45	50→55	linear gradient
10–16	45→35	55→65	linear gradient
16–25	35	65	isocratic

In-Process Revision

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
25–26	35→50	65→50	linear gradient
26–35	50	50	re-equilbration

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 1.2 for nefazodone related compound B; the resolution, *R*, between nefazodone related compound A and nefazodone hydrochloride is not less than 1.5 and is not less than 4.0 between nefazodone hydrochloride and nefazodone related compound B. Chromatograph the *Standard solution* into the chromatograph, and measure the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0% for nefazodone related compound A and nefazodone related compound B.

Procedure—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 nefazodone related compound in the portion of Nefazodone 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 the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration of Nefazodone Hydrochloride, in mg per mL, in the *Test solution;* and r_U and r_S are the peak areas of the corresponding nefazodone related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.2% of nefazodone related compound A is found; not more than 0.2% of nefazodone related compound B is found; not more than 0.1% of any unknown impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Use the peak area for nefazodone hydrochloride in the *Standard solution* as r_S to calculate any unknown impurity.]

Organic volatile impurities, *Method I* ⟨467⟩**:** meets the requirements.

Assay—Dissolve about 800 mg of Nefazodone Hydrochloride, accurately weighed, in 50 mL of glacial acetic acid, and add 15 mL of 3% (v/v) mercuric acetate in glacial acetic acid. 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 VS is equivalent to 50.65 mg of $C_{25}H_{32}ClN_5O_2 \cdot HCl$. ■2S *(USP29)*

BRIEFING

Nefazodone Hydrochloride Tablets. Because there is no existing *USP* monograph for Nefazodone Hydrochloride Tablets, a new monograph is proposed based on the validation data received. The test for *Related compounds* and the *Assay* test were developed using Waters Symmetry brand of L1 column. Nefazodone related compound A has a retention time of about 12 minutes, nefazodone hydrochloride has a retention time of about 13 minutes, and nefazodone related compound B has a retention time of about 18 minutes.

(PA3: R. Ravichandran; NL: L. Paul; PSD: C. Okeke; BPC: M. Marques) RTS—41818-2; 41818-5; 41818-6; 41818-7

In-Process Revision

Add the following:

■Nefazodone Hydrochloride Tablets

» Nefazodone Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nefazodone hydrochloride ($C_{25}H_{32}ClN_5O_2 \cdot HCl$).

Packaging and storage—Preserve in tight containers. Store between 15° and 30°.

USP Reference standards ⟨11⟩**—***USP Nefazodone Hydrochloride RS. USP Nefazodone Related Compound A RS. USP Nefazodone 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.*

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Standard stock solution—Transfer about 70 mg of USP Nefazodone Hydrochloride RS, accurately weighed, to a 50-mL volumetric flask. Add 2.5 mL of methanol, dilute with *Medium* to volume, and mix.

Standard solution—Dilute the *Standard stock solution* with *Medium* in such a way that the final concentration is similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test passed through a 0.45-µm PVDF filter, discarding the first 5 mL.

Procedure—Determine the percentage of the labeled amount of nefazodone hydrochloride dissolved by employing UV absorption, using a suitable spectrophotometer, at the wavelength of maximum absorbance at about 246 nm, on the *Test solution* in comparison with the *Standard solution*, using the *Medium* as blank. Calculate the percentage of nefazodone hydrochloride dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the USP Nefazodone Hydrochloride RS in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of nefazodone hydrochloride is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Diluted acetic acid, Buffer solution, Mobile phase, Nefazodone related compound A stock solution, Nefazodone related compound B stock solution, System suitability preparation, 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 stock preparation,* prepared as directed in the *Assay.*

In-Process Revision

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 individual nefazodone related compounds in the portion of Tablets taken by the formula:

$$100(r_U / r_S)(C_S / C_T)(1/F)$$

in which r_U is the individual peak response for each nefazodone related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution,* respectively; C_S and C_T are the concentrations, in mg per mL, of nefazodone hydrochloride in the *Standard solution* and *Test solution,* respectively; and F is the relative response factor obtained from *Table 1.* The related compound requirements are listed in *Table 1.*

Table 1

Related Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Nefazodone related compound A	0.9	1.0	0.2
Nefazodone related compound B	1.4	1.2	0.2
1,3-Bis[4-(3-chlorophenyl)piperzin-1-yl]propane	2.2	1.6	0.2
Unknown	—	1.0	0.1 each
Total known and unknown	—	—	0.5

Assay—

Diluted acetic acid—Prepare a mixture of acetic acid and water (1 : 1).

Buffer solution—Dissolve 0.77 g of ammonium acetate in 1 L of water. Add 1.0 mL of triethylamine, and mix well. Adjust with *Diluted acetic acid* to a pH of 7.10 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (58 : 42). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Nefazodone related compound A stock solution—Prepare a solution of USP Nefazodone Related Compound A RS in *Mobile phase* having a known concentration of about 80 µg per mL.

Nefazodone related compound B stock solution—Prepare a solution of USP Nefazodone Related Compound B RS in *Mobile phase* having a known concentration of about 80 µg per mL.

System suitability preparation—Transfer about 10 mg of USP Nefazodone Hydrochloride RS into a 10-mL volumetric flask. Add 2.0 mL of *Nefazodone related compound A stock solution* and 2.0 mL of *Nefazodone related compound B stock solution,* and mix to dissolve the nefazodone hydrochloride. Dilute with *Mobile phase* to volume, and mix.

Standard preparation—Prepare a solution of USP Nefazodone Hydrochloride RS in *Mobile phase* having a known concentration of about 0.1 mg per mL.

Assay stock preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg of nefazodone hydrochloride, to a 250-mL volumetric flask, add

about 125 mL of *Mobile phase*, and sonicate for about 10 minutes with occasional shaking. Dilute with *Mobile phase* to volume, and mix to obtain a solution having a concentration of about 1 mg per mL of nefazodone hydrochloride. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate, which has a concentration of about 1 mg per mL of nefazodone hydrochloride.

Assay preparation—Transfer 5.0 mL of *Assay stock preparation* into a 50-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix to obtain a solution having a concentration of 0.1 mg per mL of nefazodone hydrochloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column containing 5-µm L1 packing. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Inject the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 1.4 for nefazodone related compound B; the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 1.5, and the resolution, *R,* between nefazodone related compound B and nefazodone hydrochloride is not less than 2.0. Inject the *Standard preparation,* 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 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 percent of label claim, of nefazodone hydrochloride ($C_{25}H_{32}ClN_5O_2 \cdot HCl$) in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of nefazodone hydrochloride in the *Standard preparation* and *Assay preparation,* respectively; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

BRIEFING

Nitrous Oxide, *USP 28* page 1388, page 3264 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 707 of *PF* 31(3) [May–June 2005]—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-5

Change to read:

» Nitrous Oxide contains not less than 99.0 percent, ~~by volume~~

■volume/volume,■2S (*USP29*) of N_2O.

Change to read:

Packaging and storage—~~Preserve in cylinders.~~

■Preserve in blue cylinders. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)

In-Process Revision

NOTE—The following tests are designed to reflect the quality of Nitrous Oxide in both the vapor and liquid phases that are present in previously unopened cylinders. Reduce the container pressure by means of a regulator. Withdraw the samples for the tests with the least possible release of Nitrous Oxide consistent with proper purging of the sampling apparatus. Measure the gases with a gas volume meter downstream from the detector tubes in order to minimize contamination or change of the specimens. Perform tests in the sequence in which they are listed.

The various detector tubes called for in the respective tests are listed under *Reagents* in the section *Reagents, Indicators, and Solutions*.

Change to read:

Assay—Introduce a specimen of Nitrous Oxide taken from the liquid phase, as directed in the test for *Nitrogen dioxide,* into a gas chromatograph by means of a gas-sampling valve. Select the operating conditions of the gas chromatograph such that the peak response resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of N_2 and O_2 from N_2O, although the N_2 and O_2 may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •~~USP Air–Helium RS~~•.

■USP Nitrous Oxide RS,■2S (*USP29*)
and is equivalent to not more than 1.0% of air when compared to the peak response of the •USP Air–Helium RS,•3 indicating not less than 99.0%, by volume, of N_2O.

■•(Postponed indefinitely)•3 ■2S (*USP29*)

BRIEFING

Omeprazole, *USP 28* page 1416. It is proposed to add a note clarifying the preparation of ammonia-saturated dichloromethane for *Method 1* in the test for *Chromatographic purity.*

(PA4: E. Gonikberg) RTS—42575-1

Change to read:

Chromatographic purity—

METHOD 1—

Solvent—Prepare a mixture of dichloromethane and methanol (1 : 1).

Standard solutions—Dissolve an accurately weighed quantity of USP Omeprazole RS in *Solvent,* and mix to obtain *Standard solution A* having a known concentration of about 0.5 mg per mL. Dilute this solution quantitatively with *Solvent* to obtain *Standard solution B* and *Standard solution C* having known concentrations of about 0.15 mg per mL and 0.05 mg per mL, respectively.

Test solution—Prepare a solution of Omeprazole in *Solvent* containing 50 mg per mL.

Identification solution—Dilute a volume of the *Test solution* quantitatively with *Solvent* to obtain a solution containing 0.25 mg per mL.

Procedure—Separately apply 10 µL of the *Test solution,* the *Identification solution,* and each of the *Standard solutions* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of ammonia-saturated dichloromethane, dichloromethane, and isopropyl alcohol (2 : 2 : 1) until the solvent front has moved about three-fourths of the length of the plate.

■[NOTE—Prepare ammonia-saturated dichloromethane as follows: shake 100 mL of dichloromethane with 30 mL of ammonium hydroxide in a separatory funnel, allow the layers to separate, and use the lower layer.]■2S (*USP29*)
Remove the plate from the developing chamber, mark the solvent front, allow the solvent to evaporate, and examine the plate under short-wavelength UV light: the chromatograms show principal spots at about the same R_F value. Estimate the intensities of any secondary spots observed in the chromatogram of the *Test solution* by comparison with the spots in the chromatograms of the *Standard solutions:* no secondary spot from the chromatogram of the *Test solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.3%), and the sum of the intensities of all secondary spots obtained from the *Test solution* is no more intense than the principal spot obtained from *Standard solution A* (1.0%).

METHOD 2—

Diluent—Use *Mobile phase.*

Phosphate buffer, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Dissolve an accurately weighed quantity of Omeprazole in *Diluent* to obtain a solution containing about 0.16 mg per mL. [NOTE—Prepare this solution fresh.]

Procedure—Inject equal volumes (about 40 µL) of the *Test solution* and *Diluent* into the chromatograph, and allow the *Test solution* to elute for not less than two times the retention time of omeprazole. Record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Omeprazole 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 0.3% of any individual impurity is found, and the sum of all impurities is not more than 1.0%.

In-Process Revision

BRIEFING

Ondansetron Orally Disintegrating Tablets, page 2024 of *PF* 30(6) [Nov.—Dec. 2004]. It is proposed to add a *Disintegration* test and a *Dissolution* test to this new monograph.

(BPC: M. Marques) RTS—42415-1

Add the following:

■Ondansetron Orally Disintegrating Tablets

» Ondansetron Orally Disintegrating Tablets contain the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ondansetron ($C_{18}H_{19}N_3O$).

Packaging and storage—Preserve in light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Ondansetron RS. USP Ondansetron Related Compound A RS. USP Ondansetron Related Compound D 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.*

Disintegration: not more than 10 seconds.

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 10 minutes.

Standard solution—Accurately weigh an amount of USP Ondansetron RS, and dilute with *Medium* to obtain a solution having a final concentration of 0.01 mg per mL for Tablets labeled to contain 4 mg, and a final concentration of 0.02 mg per mL for Tablets labeled to contain 8 mg.

Test solution—Pass a portion of the solution under test through a filter.

Procedure—Determine the amount of $C_{18}H_{19}N_3O$ dissolved by UV absorption at the wavelength of maximum absorbance at about 310 nm on portions of the *Test solution* in comparison with the *Standard solution*, using a 1-cm cell. Calculate the amount, in percentage, of ondansetron released by the formula:

$$\frac{A_U \times W_S \times 500 \times MW_1 \times P \times 100}{A_S \times D \times L \times MW_2}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution*, respectively; W_S is the weight, in mg, of USP Ondansetron RS taken; 500 is the volume, in mL, of *Medium; MW_1* is the molecular weight of ondansetron (293.4); *P* is the purity, expressed in decimal, of USP Ondansetron RS; 100 is the conversion factor to percentage; *D* is the dilution factor of the *Standard solution; L* is the Tablet label claim, in mg; and MW_2 is the molecular weight of ondansetron hydrochloride dihydrate (365.9).

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{18}H_{19}N_3O$ is dissolved in 10 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Water ⟨921⟩**:** not more than 4.0%.

In-Process Revision

Related compounds—

Phosphate buffer—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (8 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Ondansetron related compound D solution—Dissolve an amount of USP Ondansetron Related Compound D RS in acetonitrile, and dilute stepwise with *Mobile phase* to obtain a solution having a known concentration of about 0.04 mg per mL.

2-Methylimidazole solution—Dissolve an amount of 2-methylimidazole in acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.04 mg per mL.

Standard stock solution—Dissolve an accurately weighed quantity of USP Ondansetron RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.04 mg per mL.

System suitability solution—Transfer 5.0 mL each of *Standard stock solution, 2-Methylimidazole solution,* and *Ondansetron related compound D solution,* to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Standard solution—Pipet 5.0 mL of the *Standard stock solution* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

System sensitivity solution—Pipet 10.0 mL of the *Standard solution* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer 10 Tablets to an appropriate volumetric flask so that the final concentration of ondansetron is about 400 µg per mL. Add *Mobile phase* to fill about 60% of the flask capacity. Shake by mechanical means for about 5 minutes, and dilute with *Mobile phase* to volume. Centrifuge a portion of this solution at 3000 rpm for 10 minutes. Use the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector and a 4.6-mm × 25-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 given in *Table 1;* the resolution, *R,* between ondansetron and any adjacent peak is not less than 1.5; the column efficiency is not less than 8000 theoretical plates for ondansetron; and the tailing factor for the ondansetron peak is not more than 2.0. Chromatograph the *System sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the ondansetron peak is not less than 15. 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—Inject a volume (about 20 µL) of the *Test solution* and the *Standard 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:

$$100(C/F)(V/D)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Ondansetron RS in the *Standard solution; F* is the relative response factor for each impurity as described in *Table 1; V* is the volume, in mL, of the volumetric flask used to prepare the *Test solution; D* is the amount, in mg, of ondansetron in the sample based on the labeled amount and number of Tab-

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lets taken; r_i is the peak area of any impurity in the *Test solution;* and r_S is the peak area of ondansetron in the *Standard solution:* it meets the requirements specified in *Table 1.*

Table 1

Compound Name	Relative Retention time	Relative Response Factor	Limit (%)
2-Methylimidazole	0.16	0.5	0.15
Ondansetron related compound D	0.45	1.2	0.12
Ondansetron	1.0	—	—
Individual unknown impurity	—	1.0	0.1
Total impurities	—	—	0.5

[NOTE—The run time is about 60 minutes.]

Assay—

Diluent: 0.01 N hydrochloric acid.

Phosphate buffer—Dissolve about 2.72 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 1 N sodium hydroxide or 0.5 N sodium hydroxide to a pH of 5.4.

Mobile phase—Prepare a filtered and degassed mixture of phosphate buffer and acetonitrile (52 : 48). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Ondansetron related compound A solution—Dissolve an amount of USP Ondansetron Related Compound A RS in *Diluent*, and dilute stepwise with *Diluent* to obtain a solution having a known concentration of about 0.14 mg per mL.

Assay preparation concentrated—Transfer 10 Tablets to an appropriate volumetric flask so that the final concentration is about 400 µg of ondansetron per mL. Add *Diluent* to fill about 60% of the flask capacity. Shake by mechanical means for about 5 minutes, and dilute with *Diluent* to volume. Filter a portion of this solution through a 0.45-µm polypropylene membrane, discarding the first 5 mL.

System suitability solution—Transfer 8.0 mL of *ondansetron related compound A solution* and 8.0 mL of the *Assay preparation concentrated* to a 50-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Ondansetron RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 40 µg per mL.

Assay preparation—Transfer 5.0 mL of the *Assay preparation concentrated* to a 50-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector and a 4.6-mm × 25-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 1.1 for ondansetron related compound A, and 1.0 for ondansetron; the resolution, *R,* between ondansetron related compound A and ondansetron is not less than 1.5; and the tailing factor is not more than 2.0 for the ondansetron 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 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

measure the responses for the ondansetron peaks. Calculate the quantity, in mg, of ondansetron ($C_{18}H_{19}N_3O$) in the portion of Tablets taken by the formula:

$$(10V)C(r_U / r_S)$$

in which V is the volume used to prepare the *Assay preparation concentrated;* C is the concentration, in mg per mL, of USP Ondansetron 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 (*USP29*)

BRIEFING

Oxycodone Hydrochloride Extended-Release Tablets. Because there is no existing *USP* monograph for this article, the following new monograph, which is based on submitted data, is being proposed. The liquid chromatographic procedures in the *Related compounds* test and the *Assay* are based on analyses performed with the Symmetry brand of L1 column. The typical retention times for oxycodone are about 8 minutes for the *Related compounds* test and about 4 minutes for the *Assay.*

(PA2: D. Bempong) RTS—41546-2; 41809-1

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Add the following:

■Oxycodone Hydrochloride Extended-Release Tablets

» Oxycodone Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$).

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Oxycodone RS. USP Oxycodone Related Compound A RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer a portion of powdered Tablets, equivalent to about 5 mg of oxycodone hydrochloride, to a suitable screw-capped tube, add 5 mL of chloroform, sonicate for about 30 seconds, shake for several minutes, and centrifuge. Use the clear supernatant.

Standard solution: 0.9 mg of USP Oxycodone RS per mL of chloroform.

Application volume: 20 µL.

Developing solvent solution: a mixture of acetone, toluene, ether, and ammonium hydroxide (6: 4: 1: 0.3).

Procedure—Proceed as directed in the chapter. Spray with iodoplatinate TS: the R_F value, color, and size of the principal spot obtained from the *Test solution* correspond to those obtained from the *Standard solution;* and no other spot is observed.

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.

Related compounds—

Buffer solution—Dissolve 1.5 g of sodium heptanesulfonate in 810 mL of water. Mix with 10 mL of glacial acetic acid, adjust with 5 N sodium hydroxide solution to a pH of 3.50 ± 0.05, and mix.

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 Oxycodone RS and USP Oxycodone Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 1.8 µg per mL of USP Oxycodone RS and about 1.8 µg per mL of USP Oxycodone Related Compound A RS.

Standard solution—Dissolve an accurately weighed quantity of USP Oxycodone RS in *Mobile phase,* and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.8 µg per mL.

Sensitivity test solution—Transfer 5 mL of the *Standard solution* into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 40 mg of oxycodone hydrochloride, to a 100-mL volumetric flask, add about 20 mL of a solvent consisting of methanol and acetonitrile (50 : 50), sonicate for about 10 minutes, and stir for 20 minutes. Dilute with *Buffer solution* to volume, and mix. Pass a portion of this solution through a suitable filter, and use the 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 packing L1. The column is maintained at a temperature of 50° and 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 resolution, *R*, between oxycodone related compound A and oxycodone is not less than 2.0. Chromatograph the *Standard solution,* 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%. Chromatograph the *Sensitivity test solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

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 each impurity in the portion of Tablets taken by the formula:

$$10(C/W)(1/F)(r_i / r_S)$$

in which C is the concentration, in µg per mL, of USP Oxycodone RS in the *Standard solution; W* is the weight, in mg, of oxycodone hydrochloride in the powdered Tablets taken to prepare the *Test solution; F* is the relative response factor (see *Table 1* for values); r_i is the peak response obtained for each individual impurity in the *Test solution;* and r_S is the peak response for oxycodone in the *Standard solution*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Limit (w/w, %)
Oxycodone	1.00	—	—
7, 8 Dihydro-14-hydroxycodeine (DHC)	about 0.6	0.64	0.5
14-Hydroxycodeine (HC) (Oxycodone related compound A)	about 1.2	0.78	0.5
Individual unknown impurity	—	—	0.5
Total impurities	—	—	2.0

Assay—

Buffer solution—Dissolve 1.5 g of sodium heptanesulfonate in 740 mL of water. Mix with 10 mL of glacial acetic acid, adjust with 5 N sodium hydroxide solution to a pH of 3.50 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (75 : 25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Oxycodone RS in *Mobile phase,* and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.036 mg per mL.

Assay stock preparation—Transfer 10 Tablets into an appropriate volumetric flask, add a volume of a mixture of methanol and acetonitrile (50 : 50) equivalent to 50% of the volumetric flask volume, sonicate for about 10 minutes, and stir for about 20 minutes. Dilute with *Buffer solution* to volume, and mix.

Assay preparation—Transfer a volume of the *Assay stock preparation,* equivalent to 4 mg of oxycodone hydrochloride into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of the solution through a suitable filter, and use the 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 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 efficiency is not less than 4000 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 measure the responses for the oxycodone peak. Calculate

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the quantity, in mg, of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the portion of Tablets taken by the formula:

$$(351.82/315.37)CD(r_U/r_S)$$

in which 351.82 and 315.37 are the molecular weights of oxycodone hydrochloride and oxycodone base, respectively; *C* is the concentration, in mg per mL, of USP Oxycodone RS in the *Standard preparation; D* is the dilution factor, in mL, for the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

BRIEFING

Oxygen, *USP 28* page 1442—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-6

Change to read:

» Oxygen contains not less than 99.0 percent, ~~by volume,~~

■volume/volume,■2S (*USP29*)
of O_2. [NOTE—Oxygen that is produced by the air-liquefaction process is exempt from the requirements of the tests for *Carbon dioxide* and *Carbon monoxide*.]

Change to read:

Packaging and storage—~~Preserve in cylinders or in a pressurized storage tank.~~

■Preserve in green cylinders or in a green pressurized storage tank. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)
Containers used for Oxygen must not be treated with any toxic, sleep-inducing, or narcosis-producing compounds, and must not be treated with any compound that will be irritating to the respiratory tract when the Oxygen is used.

NOTE—Reduce the container pressure by means of a regulator. Measure the gases with a gas volume meter downstream from the detector tube in order to minimize contamination or change of the specimens.

BRIEFING

Oxygen 93 Percent, *USP 28* page 1443—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-7

Change to read:

» Oxygen 93 Percent is Oxygen produced from air by the molecular sieve process. It contains not less than 90.0 percent and not more than 96.0 percent, ~~by volume,~~

■volume/volume,■2S (*USP29*)
of O_2, the remainder consisting mostly of argon and nitrogen.

Change to read:

Packaging and storage—~~Preserve in cylinders or in a low-pressure collecting tank.~~

■Preserve in green cylinders or in a green low-pressure collecting tank. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*USP29*)
Containers used for Oxygen 93 Percent must not be treated with any toxic, sleep-inducing, or narcosis-producing compounds, and must not be treated with any compound that will be irritating to the respiratory tract when the Oxygen 93 Percent is used.

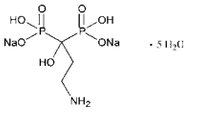
BRIEFING

Pamidronate Disodium, Pamidronate Disodium for Injection. Because there is no existing *USP* monograph for this drug substance and drug product, new monographs, based on validated methods of analysis, are being proposed. The liquid chromatographic procedures in *Test 2* for *Related compounds* and in the *Assay* are based on analyses performed with the Metrohm IC Anion Super-Sep brand of L23 column. The typical retention time for the pamidronate peak is about 8 minutes; the retention times for the phosphate and phosphite peaks are about 10 and 15 minutes, respectively. Please note that these retention times could be affected strongly by the small variations in the amounts of formic acid in the *Mobile phase*.

(PA4: E. Gonikberg; PSD: C. Okeke; NL: L. Paul; AMB: R. Tirumalai) RTS—33667-1

Add the following:

■Pamidronate Disodium



$C_3H_9NNa_2O_7P_2 \cdot 5H_2O$ 369.11

Phosphonic acid, (3-amino-1-hydroxypropylidene)bis-, disodium salt, pentahydrate.

Disodium dihydrogen (3-amino-1-hydroxypropylidene)diphosphonate, pentahydrate [*109552-15-0*].

Anhydrous [*57248-88-1*].

» Pamidronate Disodium contains not less than 98.0 percent and not more than 102.0 percent of $C_3H_9NNa_2O_7P_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers. Store at a temperature not exceeding 30°.

USP Reference standards ⟨11⟩**—***USP Beta Alanine RS. USP Pamidronate Disodium RS.*

Clarity and color of solution—

Test preparation 1—Dissolve 1.0 g of it in 50 mL of water with gentle warming. Cool to room temperature.

Test preparation 2—Dissolve 1.0 g of it in 25 mL of 2 N sodium hydroxide solution with gentle warming. Cool to room temperature.

Procedure—Examine *Test preparation 1* and *Test preparation 2:* the solutions are clear. Separately measure the absorbance of each of these solutions at 420 nm in 4-cm cells, using water as the blank for *Test preparation 1* and using 2 N sodium hydroxide solution as a blank for *Test preparation 2*: the absorbance of each solution is not more than 0.10.

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 pyroantimonate precipitate test for *Sodium* ⟨191⟩.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined yeasts and molds count does not exceed 100 cfu per g.

pH ⟨791⟩**:** between 7.8 and 8.8, in a solution (1 in 100).

Water, *Method I* ⟨921⟩**:** between 23.0% and 25.5%.

Heavy metals, *Method II* ⟨231⟩**:** 20 µg per g.

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Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Transfer 30 mg of Pamidronate Disodium to a 10-mL volumetric flask, and dissolve in and dilute with water to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Beta Alanine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.006 mg of beta alanine per mL.

Application volume: 10 µL.

Developing solvent system: a mixture of methanol, diisopropyl ether, and 25% ammonia (9 : 8 : 4).

Spray reagent—Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95 : 5).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate between 100° and 105° until the ammonia disappears completely. Spray with *Spray reagent,* and heat between 100° and 105° for about 15 minutes. Examine the plate under white light. The spot having an R_F value of about 0.5 obtained from the *Test solution* is not greater in size or intensity than the corresponding spot obtained from the *Standard solution:* not more than 0.2% of beta alanine is found. Evaluate any other additional spot in the chromatogram of the *Test solution,* and determine the percentage of total other impurities (excluding beta alanine).

TEST 2—

Mobile phase—Proceed as directed in the *Assay.*

Impurity stock solution 1—Transfer about 300 mg of ortho-phosphoric acid, accurately weighed, to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Impurity stock solution 2—Transfer about 250 mg of phosphorous acid, accurately weighed, to 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Impurity standard solution—Transfer 2.0 mL each of *Impurity stock solution 1* and *Impurity stock solution 2* to a 50-mL volumetric flask, dilute with water to volume, and mix.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *Impurity standard solution,* and record the peak responses as directed for *Procedure:* the elution order is a phosphate peak followed by the phosphite peak; the resolution, *R,* between the two peaks is not less than 2.5; the relative standard deviation for replicate injections, determined from the phosphate peak, is not more than 10%; and the relative standard deviation for replicate injections, determined from the phosphite peak, is not more than 20%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Impurity standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of phosphates as ortho-phosphoric acid in the portion of Pamidronate Disodium taken by the formula:

$$0.2\ (W_1 / W)\ (r_U / r_S)$$

in which W_1 is the weight, in mg, of ortho-phosphoric acid taken to prepare the *Impurity stock solution 1; W* is the weight, in mg, of Pamidronate Disodium taken to prepare the *Test solution;* and r_U and r_S are the responses of phosphate peaks obtained from the *Test solution* and the *Impurity standard solution*, respectively: not more than 0.5% of phosphate, determined as ortho-phosphoric acid, is found.

Calculate the percentages of phosphites as phosphorous acid in the portion of Pamidronate Disodium taken by the formula:

$$0.2\ (W_2/W)\ (r_U/r_S)$$

in which W_2 is the weight, in mg, of phosphorous acid taken to prepare the *Impurity stock solution 1; W* is defined above; and r_U and r_S are the responses of phosphite peaks obtained from the *Test solution* and the *Impurity standard solution,* respectively: not more than 0.5% of phosphite, determined as phosphorous acid, is found, and not more than 0.5% of total phosphate and phosphite combined is found.

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

$$0.2\ (W_1/W)\ (r_i/r_S)$$

in which W_1 and W are defined above; r_i is the peak response of any other impurity in the *Test solution; and* r_S is the response of the phosphate peak obtained from the *Impurity standard solution:* not more than 0.5% of total other impurities (excluding beta alanine, phosphate as ortho-phosphoric acid, and phosphite as phosphorous acid) is found, the results for *Test 1* and *Test 2* being added.

Alcohol content, *Method II* ⟨611⟩: not more than 0.3% is found.

Assay—

Mobile phase—To 2500 mL of water, add 0.47 mL of anhydrous formic acid, adjust with 2 N sodium hydroxide solution to a pH of 3.5, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—The small amounts of formic acid have a strong influence on the retention times.]

Standard preparation—Dissolve an accurately weighed quantity of USP Pamidronate Disodium RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 2 mg per mL.

Assay preparation—Transfer about 100 mg of Pamidronate Disodium, 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 refractive index detector and a 4.6-mm × 10-cm column that contains packing L23. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not less than 0.3 and 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 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 $C_3H_9NNa_2O_7P_2$ in the portion of Pamidronate Disodium taken by the formula:

$$50C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Pamidronate Disodium 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 (*USP29*)

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BRIEFING

Pamidronate Disodium for Injection—See briefing under *Pamidronate Disodium.*

(PA4: E. Gonikberg; PSD: C. Okeke; NL: L. Paul; AMB: R. Tirumalai) RTS—33667-2

Add the following:

■Pamidronate Disodium for Injection

» Pamidronate Disodium for Injection is a sterile, freeze-dried mixture of Pamidronate Disodium and suitable excipients. It contains not less than 98.0 percent and not more than 108.0 percent of the labeled amount of pamidronate disodium ($C_3H_9NNa_2O_7P_2$).

Packaging and storage—Preserve in *Containers for Sterile Solids,* as described under *Injections* ⟨1⟩, preferably of Type III glass. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Beta Alanine RS. USP Endotoxin RS. USP Pamidronate Disodium RS.*

Constituted solution—At the time of use, it meets the requirements for *Constituted Solutions* under *Injections* ⟨1⟩.

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 2 USP Endotoxin Units per mg of anhydrous pamidronate disodium.

Uniformity of dosage units ⟨905⟩**:** meets the requirements for *Weight Variation.*

pH ⟨791⟩**:** between 6.0 and 7.0, determined in a solution constituted as directed in the labeling.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Sterility Tests* ⟨71⟩ and *Labeling* under *Injections* ⟨1⟩.

Water, *Method Ia* ⟨921⟩**:** not more than 5%.

Limit of beta alanine—

Adsorbent, Application volume, Developing solvent system, and *Spray reagent*—Proceed as directed under the *Related compounds, Test 1* for *Pamidronate Disodium.*

Standard solution—Dissolve an accurately weighed quantity of USP Beta Alanine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.0075 mg of beta alanine per mL.

Test solution—Reconstitute the vial with the appropriate amount of water to achieve a solution having a concentration of 3 mg of anhydrous pamidronate disodium per mL, based on the label claim.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate between 100° and 105° until the ammonia disappears completely. Spray with *Spray reagent,* and heat between 100° and 105° for about 15 minutes. Examine the plate under white light. The spot having an R_F value of about 0.5 obtained from the *Test solution* is not greater in size or intensity than the corresponding spot obtained from the *Standard solution:* not more than 0.25% of beta alanine is found.

Assay—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay* under *Pamidronate Disodium.*

Standard preparation—Dissolve an accurately weighed quantity of USP Pamidronate Disodium RS in water, and dilute quantitatively, and stepwise if necessary, with water

to obtain a solution having a known concentration of about 2.5 mg per mL. Calculate the concentration, *C,* of anhydrous pamidronate disodium; the molecular weights of anhydrous and pentahydrate pamidronate disodium being 279.06 and 369.11, respectively.

Assay preparation—Constitute a suitable number of vials of Pamidronate Disodium for Injection with the appropriate amount of water to obtain a solution having a known concentration of about 2 mg of anhydrous pamidronate disodium per mL, based on the label claim.

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 $C_3H_9NNa_2O_7P_2$ in the portion of Pamidronate Disodium for Injection taken by the formula:

$$50C(r_U / r_S)$$

in which C is as defined under the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

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BRIEFING

Paroxetine Hydrochloride, *USP 28* page 1474 and page 69 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to rename the Reference Standards used in this monograph. USP Paroxetine Hydrochloride System Suitability RS is being renamed as USP Paroxetine System Suitability Mixture A RS. USP Paroxetine Related Compound E RS is being renamed as USP Paroxetine Related Compound E Mixture RS. The *USP Reference standards* section is being revised to reflect this change.

(PA3: R. Ravichandran) RTS—42643-1

Change to read:

USP Reference standards ⟨11⟩—*USP Paroxetine Hydrochloride RS.* ~~*USP Paroxetine Related Compound A RS.*~~

~~*USP Paroxetine Hydrochloride for System Suitability RS.*~~

■*USP Paroxetine System Suitability Mixture A RS.*■2S (*USP29*)
USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS. ~~*USP Paroxetine Related Compound E RS.*~~

■*USP Paroxetine Related Compound E Mixture RS.*■2S (*USP29*)
USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.

Change to read:

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 100 ng per mL.~~ ■~~20 ng per mL.~~■1S (*USP29*)

~~*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 responses for the ma-~~

~~jor peaks. Calculate the amount, in 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, 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 20 ng is found (0.0001%).~~

■*Solution A*—Dissolve about 30 g of sodium perchlorate in about 900 mL of water. Add 3.5 mL of phosphoric acid and 2.4 mL of triethylamine. Dilute with water to volume, and mix. Adjust with phosphoric acid or triethylamine to a pH of 2.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution B: acetonitrile, filtered and degassed.

Diluent: a mixture of water and acetonitrile (4 : 1).

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 solution—Dissolve an accurately weighed quantity of ~~USP Paroxetine Hydrochloride Related Compound E RS,~~ USP Paroxetine Related Compound E Mixture RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 42 ng per mL of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine.

Test solution—Transfer about 420 mg of Paroxetine Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve in about 7 mL of *Diluent* with sonication. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 242-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	85	15	equilibration
0–20	85→80	15→20	linear gradient
20–27	80→55	20→45	linear gradient
27–36	55	45	isocratic
36–38	55→80	45→15	linear gradient
38–45	85	15	re-equilibration

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative retention times are 0.6 for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine and 1.0 for paroxetine; and the relative standard deviation for replicate injections is not more than 15.0% for the 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine peak.

Procedure—Separately inject equal volumes (about 75 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 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$1000(CI/W)\ (r_i / r_s)$$

in which *C* is the concentration, in mg per mL, of ~~USP Paroxetine Hydrochloride Related Compound E RS~~ USP Paroxetine Related Compound E Mixture RS in the *Standard solution; I* is the fraction, by weight, of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in ~~USP Paroxetine Hydrochloride Related Compound E RS;~~ USP Paroxetine

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Hydrochloride Related Compound E Mixture RS; *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 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine obtained from the *Test solution* and the *Standard solution,* respectively: not more than of 0.0001% of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine is found.■2S (*USP29*)

Change to read:

Chromatographic purity—[NOTE—Perform 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 *Diluent* to obtain a solution having known concentrations of about 0.01 mg of each USP Reference Standard per mL.~~

■Dissolve, by sonication if necessary, a suitable quantity of ~~USP Paroxetine Hydrochloride for System Suitability RS~~ USP Paroxetine System Suitability Mixture A RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.■2S (*USP29*)

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in 20 mL of *Diluent,* sonicate, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector 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 relative retention times are about ~~1.1 for paroxetine related compound B, and 1.0 for paroxetine related compound A~~

■0.66 for paroxetine related compound A, 0.73 for paroxetine related compound B, and 1.0 for paroxetine;■2S (*USP29*) 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; 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,* the *Test solution,* and the *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 from the chromatogram of the *Diluent;* and r_S is the peak area of paroxetine obtained from the *Standard solution:* not more than of 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 L 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 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 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* 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.

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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 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.

BRIEFING

Sodium Polystyrene Sulfonate Suspension, *USP 28* page 1793. It is proposed to remove the reference to *Sorbitol* as a component of this dosage form. This revision was prompted by safety concerns. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 28–NF 23,* with an official date of October 1, 2005.

(RMI: A. Wilk) RTS—42353-1

Change to read:

» Sodium Polystyrene Sulfonate Suspension is a suspension of Sodium Polystyrene Sulfonate in an aqueous vehicle ~~containing a suitable quantity of sorbitol. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sorbitol ($C_6H_{14}O_6$), and~~

•that may contain suitable suspending or stabilizing agents. It•5
exchanges not less than 110 mg and not more than 135 mg of potassium for each g of the labeled amount of sodium polystyrene sulfonate.

Delete the following:

•~~**Labeling**—Label it to state the quantity of sorbitol in a given volume of Suspension.~~•5

Delete the following:

•~~**USP Reference standards** ⟨11⟩—*USP Sorbitol RS*~~•5

Delete the following:

•~~**Assay for sorbitol**—~~

~~*Mobile phase, Resolution solution, Standard preparation,* and *Chromatographic system*—Proceed as directed in the *Assay* under *Sorbitol* (see *NF* monograph).~~

~~*Assay preparation*—Dilute an accurately measured volume of Suspension, freshly mixed and free from air bubbles, quantitatively with water to obtain a solution containing about 4.8 mg of sorbitol per mL. Filter, and use the filtrate as the *Assay preparation.*~~

~~*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 responses for the major peaks. Proceed as directed for *Procedure* in the *Assay* under *Sorbitol* (see *NF* monograph). Calculate the quantity, in g, of $C_6H_{14}O_6$, in each mL of the Suspension taken by the formula:~~

~~$$(L / D)(C)(r_U / r_S),$$~~

~~in which L is the labeled quantity, in g, of sorbitol in each mL of Suspension; D is the quantity, in mg, of sorbitol in each mL of the~~

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~~*Assay preparation* based on the labeled quantity and the extent of dilution; *C* is the concentration, in mg per mL, of *USP Sorbitol 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.~~ •5

BRIEFING

Sodium Salicylate Tablets, *USP 28* page 1794. It is proposed to revise the monograph to include USP Sodium Salicylate RS, to be used in the preparation of the Standard solution specified in the *Dissolution* test.

(PA2: D. Bempong) RTS—42612-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Sodium Salicylate RS.* ■2S (*USP29*)

BRIEFING

Tazobactam. 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 procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Partisil ODS-3 brand of L1 column. It is noted that if an autosampler is used, the plastic tubing connected to the injection needle should be replaced with a stainless steel assembly to eliminate absorption of tazobactam on the plastic tubing. In the test for *Related compounds,* the typical retention times for tazobactam related compound A and tazobactam are about 2.8 and 10 minutes, respectively. In the *Assay,* the typical retention times for L-phenylalanine (resolution compound) and tazobactam are about 7 and 10 minutes, respectively.

(PA7a: B. Gilbert) RTS—40762-1

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Add the following:

■Tazobactam

$C_{10}H_{12}N_4O_5S$ 300.29

4-Thia-1-azobicyclo[3.2.0]heptane-2-carboxylic acid, 3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, [2*S*-(2α,3β,5α)]-.

(2*S*,3*S*,5*R*)-3-Methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide [*89786-04-9*].

» Tazobactam contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}N_4O_5S$ calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Tazobactam RS. USP Tazobactam Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩, on an undried specimen.

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⟩**—**[To come.]

Specific rotation ⟨781S⟩**:** between +60° and +167° (*t* = 20°).

Test solution: 10 mg per mL, in dimethylformamide.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

pH ⟨791⟩**:** between 1.8 and 2.8, in a solution containing 2.5 mg per mL.

Water, *Method I* ⟨921⟩**:** not more than 0.6%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Mobile phase, L-Phenylalanine solution, System suitability solution, and *Chromatographic system*—Prepare as directed in the *Assay.*

Blank—Use water.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Procedure—Cool and maintain the *Standard solution*, the *System suitability solution,* the *Blank,* and the *Test solution* at 3° until injection. [NOTE—If an autosampler is used, replace the plastic tubing connected to the injection needle with a stainless steel assembly, and maintain at 3°.] Separately inject equal volumes (about 20 µL) of the *Standard solution*, the *System suitability solution,* the *Blank,* and the *Test solution* into the chromatograph; record the chromatograms; and measure the area responses for the peaks. Calculate the percentage of each related substance in the portion of Tazobactam taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response for each related compound in the chromatogram obtained from the *Test solution,* and r_s is the sum of the peak responses of all the peaks in the chromatogram obtained from the *Test solution:* not more than 1.0% of tazobactam related compound A is found; and the sum of all impurities found, other than tazobactam related compound A, is not greater than 0.3%. [NOTE—Ignore any peaks in the chromatogram of the *Test solution* that correspond to any peaks seen in the chromatogram of the *Blank.*]

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Assay—

Mobile phase—Dissolve 1.32 g of dibasic ammonium phosphate in 750 mL of water. Adjust with 5% v/v phosphoric acid to a pH of 2.5, dilute with water to 1000 mL, and mix. Add 30 mL of acetonitrile, mix, and pass through a filter having 0.2-µm porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Tazobactam RS and USP Tazobactam Related Compound A RS in water to obtain a solution having known concentrations of about 0.5 mg per mL and 0.08 mg per mL, respectively.

L-Phenylalanine solution—Prepare an aqueous solution of L-phenylalanine containing 0.8 mg per mL.

System suitability solution—Pipet 1.0 mL of *L-Phenylalanine solution* and 5.0 mL of the *Standard preparation* into a 50-mL volumetric flask. Dilute with water to volume, and mix. [NOTE—Maintain this solution at 3° until injection. Prepare fresh daily.]

Assay preparation—Transfer about 25 mg of Tazobactam, 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 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm

packing L1. The flow rate is about 1.5 mL per minute. Chromatograph 20 µL of the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tazobactam and L-phenylalanine is not less than 6.0; the tailing factor is not more than 1.8; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Cool and maintain the *Standard preparation*, the *System suitability solution*, and the *Assay preparation* at 3° until injection. [NOTE—If an autosampler is used, replace the plastic tubing connected to the injection needle with a stainless steel assembly, and maintain at 3°.] 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 $C_{10}H_{12}N_4O_5S$ in the portion of Tazobactam taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Tazobactam 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 (*USP29*)

BRIEFING

Tolazamide, *USP 28* page 1945. It is proposed to revise the test for *Chromatographic purity* to correct the relative retention time for the specified impurity (*p*-toluenesulfonic acid) and to modify the calculation procedure.

(PA4: E. Gonikberg) RTS—42605-1

Change to read:

Chromatographic purity—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (100 : 100 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve an accurately weighed quantity of USP Tolazamide RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.014 mg per mL.

Test solution—[NOTE—Make solution fresh before each injection.] Transfer about 140 mg of Tolazamide, accurately weighed, to a 100-mL volumetric flask, dissolve in *Mobile phase*, sonicating if necessary, 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 3.9-mm × 30-cm column that contains 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 column efficiency is not less than 4000 theoretical plates; the tailing factor is not more than 3.0; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Inject a volume (about 50 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tolazamide taken by the formula:

~~$100r_i/(\Sigma r_i + r_s)$,~~

■$100(1/F)(r_i / r_s)$■2S (*USP29*)

in which F is the relative response factor, which is equal to ~~2 for any peak having~~

■0.52 for the *p*-toluenesulfonic acid peak eluting at■2S (*USP29*) a relative retention time of ~~0.03~~

■0.23■2S (*USP29*) and equal to 1.0 for all other peaks; r_i is the peak response for each impurity; and ~~r_s is the tolazamide peak response:~~

■r_s is the sum of the responses of all peaks:■2S (*USP29*) not more than 0.5% of any individual impurity is found; and not more than 1.5% of total impurities is found.

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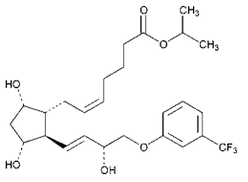
BRIEFING

Travoprost. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed based on manufacturer's tests and acceptance criteria. The reverse phase HPLC procedures for the *Related compounds* and *Assay* tests were validated using a Hypersil C18 brand of L1 column; travoprost elutes at approximately 36.5 minutes.

(PA6: L. Evans; PSD: C. Okeke; NL: L. Paul) RTS—41201-1; 42060-1

Add the following:

■Travoprost



$C_{26}H_{35}F_3O_6$ 500.55

[1*R*-[1α(*Z*),2*β*(1*E*,3*R**),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester.

(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-isopropyl-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate [*157283-68-6*].

» Travoprost contains not less than 96.0 percent and not more than 102.0 percent of $C_{26}H_{35}F_3O_6$, calculated on the anhydrous basis.

Caution—Great care should be taken to avoid inhalation and contact with the body.

Packaging and storage—Preserve at –25° to –15° in tight, light-resistant containers under a nitrogen atmosphere.

USP Reference standards ⟨11⟩—*USP Travoprost RS.*

Identification—

A: *Infrared Absorption* ⟨197F⟩.

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 Ia* ⟨921⟩**:** not more than 1.0%, determined on a 0.2-g specimen. Use a solvent mixture of acetontrile and methanol (1 : 1) and a titrant for which 1 mL is equivalent to 2 mg of water.

Specific rotation ⟨781S⟩**:** from +52.0° to +58.0°, at 365 nm.

Test solution: 20 mg per mL, in ethyl alcohol, absolute.

Related compounds—

Buffer, Mobile phase, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Inject a volume (about 100 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 Travoprost taken by the formula:

$$100(1/F)(r_i / r_s)$$

in which F is the relative response factor for each impurity, r_i is the individual peak response of each individual impurity, and r_s is the sum of the responses of all the peaks. In addi-

tion 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 4 .0 % of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
acid derivative[1]	about 0.11	1.0	0.2
epoxide derivative[2]	about 0.55	1.0	0.4
15-*epi* diastereomer[3]	about 0.90	1.0	0.1
5,6-*trans* isomer[4]	about 1.16	1.0	3.5
15-keto derivative[5]	about 1.45	1.6	0.3

[1] acid derivative — (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid
[2] epoxide derivative — (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-12, 13-dihydroepoxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester;
[3] 15-epi diastereomer — (5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester
[4] 5,6-trans isomer — (5*E*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester
[5] 15-keto derivative — (5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,-Dihydroxy-15-oxo-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester

Limit of ethyl acetate—

Standard solution—Dilute an accurately measured quantity of ethyl acetate in *N,N*-dimethylacetamide to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Travoprost in *N,N*-dimethylacetamide to obtain a solution having a concentration of about 20 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-m × 30-m column coated with a 1-µm film of liquid phase G16. The carrier gas is helium, flowing at a rate of 4 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 55° for 6 minutes, then the temperature is increased at a rate of 25° per minute to 240°, and held at 240° for 20 minutes. The injection port temperature is maintained at 140°, and the detector temperature is maintained at 240°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time is about 3.5 minutes for ethyl acetate; the resolution, *R,* between ethyl acetate and any adjacent peak is not less than 1.5; and the relative standard deviation for replicate injections is not more than 15.0%.

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 concentration, in ppm, of ethyl acetate in the portion of Travoprost taken by the formula:

$$C_S / C_U (r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of ethyl acetate in the *Standard solution;* C_U is the concentration, in g per mL, of Travoprost 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 5000 ppm of ethyl acetate is found.

Assay—

Buffer—Add 2.0 mL of phosphoric acid to 1 L of water. Adjust with sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Use USP Travopost RS without dilution (0.5 mg per mL).

In-Process Revision

Assay preparation—Transfer about 25 mg of Travoprost, accurately weighed, to a 50-mL volumetric flask, and dissolve in 15 mL of acetonitrile. Add 25 mL of water, mix, and wait until the solution reaches room temperature. Dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between travoprost and any adjacent peak is not less than 1.5; the column efficiency is not less than 1500 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 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 $C_{26}H_{35}F_3O_6$ in the portion of Travoprost taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost 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 (*USP29*)

BRIEFING

Travoprost Ophthalmic Solution. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed based on manufacturer's tests and acceptance criteria. The reverse phase HPLC procedures for the *Limit of degradation products* and *Assay* tests were validated using a Discovery C18 brand of L1 column; travoprost elutes at aprroximately 38.9 minutes. The reverse phase HPLC procedure for the *Limit of travoprost related compound A* test was validated using a Hypersil C18 brand of L1 column; travoprost related compound A elutes at approximately 15.2 minutes.

(PA6: L. Evans; PSD: C. Okeke; NL: L. Paul; AMB: R. Tirumalai) RTS—41201-2; 42060-2

Add the following:

■Travoprost Ophthalmic Solution

» Travoprost Ophthalmic Solution is a sterile buffered aqueous solution of Travoprost. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of travoprost ($C_{26}H_{35}F_3O_6$). It may contain suitable stabilizers, buffers, and antimicrobial agents.

Caution—Great care should be taken to avoid inhalation of Travoprost and exposure to the body.

Packaging and storage—Preserve in tight, light-resistant containers. Store between 2° to 25°.

USP Reference standards ⟨11⟩**—***USP Travoprost RS. USP Travoprost Related Compound A RS.*

In-Process Revision

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.*

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩ when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

pH ⟨791⟩**:** between 5.5 and 6.5.

Limit of travoprost related compound A—

Buffer—Add 2.0 mL of phosphoric acid to 2.0 L of water Adjust with sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (19 : 6). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dilute USP Travoprost Related Compound A RS with water and acetonitrile (80 : 20), and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.3 µg of travoprost related compound A per mL.

Test solution—Use the Ophthalmic Solution without dilution.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than 10.0%.

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 quantity, in mg of USP Travoprost Related Compound A RS in each mL of the Ophthalmic Solution taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost Related Compound A RS in the *Standard solution;* and r_U and r_S are the peak responses of travoprost related compound A obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.3% is found.

Limit of degradation products—

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

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

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Measure the responses for the 5,6-*trans* isomer and 15-keto derivative. Calculate the quantity, in mg, of each degradation product in each mL, of the Ophthalmic Solution taken by the formula:

$$(C/F)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of travoprost in the *Standard solution; F* is the relative response factor for each known degradation product; r_U is the peak response for each degradation product obtained from the *Test solution;* and r_S is the travoprost peak response obtained from the *Standard solution:* not more than 5.0% of 5,6-*trans* isomer (relative retention time of about 1.1 and relative response factor, F = 1.0) and not more than 0.3% of the 15-keto derivative (relative retention time of about 1.4 and relative response factor, F = 1.7) is found; and the sum of all

In-Process Revision

degradation products, including the amount of travoprost related compound A obtained in the test for the *Limit of travoprost related compound A* is not more than 5.5%.

Assay—

Buffer—Dissolve 4.35 g of octanesulfonic acid, sodium salt in 2.0 L of water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (33 : 17). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dilute USP Travoprost RS with water and acetonitrile (7 : 3), and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg of travoprost per mL.

Assay preparation—Use the Ophthalmic Solution without dilution.

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 L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between travoprost and any adjacent peak is not less than 1.5; the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections for the travoprost peak 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 travoprost ($C_{26}H_{35}F_3O_6$) in each mL of the Ophthalmic Solution taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost 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 (*USP29*)

BRIEFING

Valsartan and Hydrochlorothiazide Tablets, page 2000 of *PF* 29(6) [Nov.–Dec. 2003]. This monograph is presented again with additional changes. It is proposed to revise the formulas for the calculation of the amounts of drug released in the test for *Dissolution.*

(BPC: M. Marques) RTS—42317-1

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.*

In-Process Revision

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 portions of the solution under test passed through a 1-µm glass fiber filter, ~~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, using a 0.2-cm quartz cell. Calculate the amount of valsartan ($C_{24}H_{29}N_5O_3$) dissolved, in percentage, 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_{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:~~

$$1000D\left(\frac{A_{\text{obs}272}a_{\text{V}250}-A_{\text{obs}250}a_{\text{V}272}}{a_{\text{V}250}a_{\text{H}272}-a_{\text{V}272}a_{\text{H}250}}\right)$$

~~in which the terms are as defined above.~~

$$\frac{(AT2\times A1\%H_{272nm})-(AT1\times A1\%H_{250nm})}{(A1\%V_{250nm}\times A1\%H_{272nm})-(A1\%V_{272nm}\times A1\%H_{250nm})}\times 12{,}500$$

In-Process Revision

Calculate the amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved, in percentage, by the formula:

$$\frac{(AT1 \times A1\%V_{250nm}) - (AT2 \times A1\%V_{272nm})}{(A1\%H_{272nm} \times A1\%V_{250nm}) - (A1\%H_{250nm} \times A1\%V_{272nm})} \times 80{,}000$$

in which $AT1$ is the absorbance of the solution under test at 272 nm; $AT2$ is the absorbance of the solution under test at 250 nm; $A1\%V_{272nm}$ is the absorptivity (1%, 0.2 cm, 272 nm) of valsartan in *Medium;* $A1\%V_{250nm}$ is the absorptivity (1%, 0.2 cm, 250 nm) of valsartan in *Medium;* $A1\%H_{272\ nm}$ is the absorptivity (1%, 0.2 cm, 272 nm) of hydrochlorthiazide in *Medium;* $A1\%H_{250nm}$ is the absorptivity (1%, 0.2 cm, 250 nm) of hydrochlorothiazide in *Medium.*

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.*

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 the *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

In-Process Revision

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 12.5J 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.

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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.■2S (*USP29*)

BRIEFING

Vasopressin, *USP 28* page 2016. It is proposed to revise *Identification* test *B* by replacing the test for *Bioidentity* with a test for *Mass spectral analysis*.

(BNT: L. Callahan) RTS—42671-1

Change to read:

Identification—

A: The retention time of the vasopressin peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

~~**B:** *Bioidentity*—About 18 hours prior to the test, select a male rat weighing between 275 g and 325 g. Inject, subcutaneously, 1 mL per kg of body weight of a solution prepared by dissolving 50 mg of phenoxybenzamine hydrochloride in 0.1 mL of alcohol, acidifying with 1 drop of hydrochloric acid, and diluting with saline TS to 5 mL. On the day of the test, anesthetize the rat, using an anesthetic substance that favors the maintenance of a uniform blood pressure. Secure the animal, and cannulate the trachea for artificial respiration. Arrange to obtain a continuous record of the blood pressure from the carotid artery. Arrange for intravenous injections by means of a suitable cannula approximately 1 mm in external diameter inserted into a femoral or jugular vein. Keep the animal warm during its preparation and during the test. Determine by trial the dose of the *Standard preparation* which, when injected intravenously at regular intervals of 12 to 15 minutes, will produce consistent blood pressure elevations of between 20 and 70 mm of mercury. Select the 2 doses that would be in a ratio of approximately 2 to 3, and prepare 2 doses of the *Test preparation* that correspond to the doses of the selected *Standard preparations*. Inject the rat with each dose in replicate of the *Standard preparation* and the *Test preparation* in a random fashion at regular intervals of 12 to 15 minutes, and record the blood pressures. The requirements of the test are met if the increase in blood pressure between the low dose and the high dose of the *Standard preparation* is comparable to that of the *Test preparation*.~~

■**B:** *Mass spectral analysis*—

Infusion solution—Prepare a mixture of acetonitrile, water, and trifluoroacetic acid (80 : 20 : 0.08).

Standard solution—Dissolve an accurately weighed quantity of USP Vasopressin RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Test solution—Dissolve an accurately weighed quantity of USP Vasopressin RS in water to obtain a solution having a known concentration of about 1 mg per mL. [NOTE—The final concentrations of the *Standard solution* and the *Test solution* can be adjusted depending on the sensitivity of the mass spectrometer used in the testing.]

In-Process Revision

Mass spectrometric system (see *Mass Spectrometry* ⟨736⟩)—The LC/MS spectrometer is equipped with an infusion system connected to an electrospray interface. The mass spectrometer is operated in the positive ion mode. [NOTE—The infusion system flow rate can be adjusted, as needed. To assist in nebulization, the infusion system can contain a sheathing gas fluid.]

Procedure—Separately inject equal volumes of the *Standard solution* and the *Test solution* (about 10 µL) into the infusion system. The flow rate for the infusion system is approximately 0.3 mL per minute. Obtain optimized mass spectra, following injection. The mass spectra of both the *Standard solution* and the *Test solution* should contain peaks with mass-to-charge ratios of 1084 and 543.■2S (*USP29*)

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 23* page 2941, page 3349 of the *First Supplement,* and page 805 of *PF* 31(3) [May–June 2005]. It is proposed to add *Maltitol* to the *Humectant, Sweetening Agent,* and *Tablet and/or Capsule Diluent* categories to complement the proposed new monograph *Maltitol*. It is also proposed to add *Amino Methacrylate Copolymer* and *Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion* to the *Coating Agent, Polymer Membrane,* and *Tablet Binder* categories to complement the proposed new monographs *Amino Methacrylate Copolymer* and *Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion,* respectively, which appear elsewhere in this issue of *PF.*

(EMC) RTS—39405-1; 40243-1; 41750-1; 41979-1; 41979-2

Add the following:

■In the following reference table, the grouping of excipients by functional category is intended to summarize the most typically identified purpose that these excipients serve in drug product formulations. The list of substances included in each category is not comprehensive. The statement of category is intended neither to limit in any way the choice or use of the substance nor to indicate that it has no other utility.■2S (*NF23*)

Change to read:

Antifoaming Agent
Dimethicone

■Myristic Acid■2S (*NF23*)
■Palmitic Acid■1S (*NF23*)
Simethicone

Change to read:

Buffering Agent
Acetic Acid
▲Adipic Acid▲*NF23*
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
▲Citric Acid, Anhydrous▲*NF23*
▲Citric Acid Monohydrate▲*NF23*
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate

■Potassium Phosphate, Dibasic■2S (*NF23*)
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
▲Succinic Acid▲*NF23*

Change to read:

Coating Agent

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
▲Cellaburate▲*NF23*
Cellulose Acetate Phthalate (see Cellacefate)
■Copovidone■1S (*NF23*)

▲Corn Syrup Solids▲*NF24*

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)

In-Process Revision

Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)

■Hypromellose Acetate Succinate■2S (*NF23*)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)

■Maltodextrin■2S (*NF23*)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
■Starch, Pregelatinized Modified■1S (*NF23*)
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Color
Caramel
Ferric Oxide, red, yellow, ~~black,~~

■■2S (*NF23*)
or blends

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Diglycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate

■Sorbitan Sesquioleate■2S (*NF23*)

■Sorbitan Trioleate■2S (*NF23*)
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Flavors and Perfumes

■Almond Oil■2S (*NF23*)
Anethole
Benzaldehyde

■Ethyl Acetate■2S (*NF23*)
Ethyl Vanillin
■Maltol■1S (*NF23*)
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

Change to read:

Humectant

▲Corn Syrup Solids▲*NF24*
Glycerin
Hexylene Glycol

■Maltitol■2S (*NF24*)
Propylene Glycol
Sorbitol

■Sorbitol Sorbitan Solution■2S (*NF23*)

▲Tagatose▲*NF24*

Change to read:

Ointment Base
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Diethylene Glycol Monoethyl Ether

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Lanolin
Ointment, Hydrophilic
Ointment, White
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Ointment, Yellow
Polyethylene Glycol ~~Ointment~~

■Monomethyl Ether■2S (*NF23*)

Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water
Squalane
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Vegetable Oil, Hydrogenated, Type II

Change to read:

Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol

■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol

■Sorbitol Sorbitan Solution■2S (*NF23*)
Triacetin
Tributyl Citrate
Triethyl Citrate

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
▲Cellaburate▲*NF23*
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■1S (*NF24*)
▲Sodium Tartrate▲*NF23*

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Peanut Oil
Polyethylene Glycol

■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol
Sesame Oil
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar

■Alamic Acid■2S (*NF23*)
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 Copolymer

▲Carbomer Homopolymer▲*NF24*
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

▲Corn Syrup Solids▲*NF24*
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate

■Maltodextrin■2S (*NF23*)
Methylcellulose
Pectin

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Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
▲Acesulfame Potassium▲*NF23*
Aspartame
Aspartame Acesulfame

▲Corn Syrup Solids▲*NF24*
Dextrates
Dextrose
Dextrose Excipient
Fructose
▲Galactose▲*NF23*

■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

▲Tagatose▲*NF24*

Change to read:

Tablet Binder
Acacia
Alginic Acid

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion

▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
■Copovidone■1S (*NF23*)

▲Corn Syrup Solids▲*NF24*
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum

■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)

■Hypromellose Acetate Succinate■2S (*NF23*)

■Maltodextrin■2S (*NF23*)
Maltose
Methylcellulose
Polyethylene Oxide
Povidone
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Syrup

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▲*NF24*
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose Monohydrate

■Maltitol■2S (*NF24*)

■Maltodextrin■2S (*NF23*)
Maltose
Mannitol
Sorbitol
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Maltose
Polacrilin Potassium
Sodium Starch Glycolate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*

Change to read:

Tablet and/or Capsule Lubricant
Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light
Polyethylene Glycol

■Polyoxyl 10 Oleyl Ether■2S (*NF23*)

■Polyoxyl 20 Cetostearyl Ether■2S (*NF23*)

■Polyoxyl 35 Castor Oil■2S (*NF23*)

■Polyoxyl 40 Hydrogenated Castor Oil■2S (*NF23*)

■Polysorbate 20■2S (*NF23*)

■Polysorbate 40■2S (*NF23*)

■Polysorbate 60■2S (*NF23*)

■Polysorbate 80■2S (*NF23*)

■Sodium Lauryl Sulfate■2S (*NF23*)
Sodium Stearyl Fumarate

■Sorbitan Monolaurate■2S (*NF23*)

■Sorbitan Monooleate■2S (*NF23*)

■Sorbitan Monopalmitate■2S (*NF23*)

■Sorbitan Monostearate■2S (*NF23*)

■Sorbitan Sesquioleate■2S (*NF23*)

■Sorbitan Trioleate■2S (*NF23*)
Stearic Acid
Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

Change to read:

Tonicity Agent

▲Corn Syrup Solids▲*NF24*
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

▲Corn Syrup Solids▲*NF24*

■Dextrose■2S (*NF23*)
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

Change to read:

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride
Docusate Sodium
Nonoxynol 9
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate

■Sorbitan Sesquioleate■2S (*NF23*)

■Sorbitan Trioleate■2S (*NF23*)
Tyloxapol

In-Process Revision

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Lutein, *USP 28* page 2112; **Lutein Preparation,** *USP 28* page 2112. It is proposed to revise the content of lutein and zeaxanthin specifications in the Definition. Revisions to the *Packaging and storage* section are also being proposed. *Identification* test *A* is being revised to account for the absorbance exhibited by the small amount of zeaxanthin present. A new normal phase HPLC procedure used in the tests for *Zeaxanthin and other related compounds* and *Content of lutein* is being proposed; it was validated using a Spherisorb CN brand of L10 column. The retention times for lutein and zeaxanthin are about 20.0 minutes and 22.6 minutes, respectively. Finally, additional revisions are being proposed in the test for *Content of total carotenoids.*

(DSN: L. Evans; PSD: C. Okeke) RTS—42699-1

Change to read:

» Lutein is the purified fraction obtained from saponification of the oleoresin of *Tagetes erecta* L. It contains not less than 80.0 percent of total carotenoids calculated as lutein ($C_{40}H_{56}O_2$). ~~It contains not less than 75.0 percent of lutein and not more than 8.0 percent of zeaxanthin, both calculated as lutein ($C_{40}H_{56}O_2$) on the anhydrous basis.~~

■It contains not less than 74.0 percent of lutein and not more than 8.5 percent of zeaxanthin, both calculated as ($C_{40}H_{56}O_2$) on the anhydrous basis.■2S (*USP29*)

Change to read:

Packaging and storage—~~Preserve in tight, light-resistant containers. Store in a cold place.~~

■Preserve in tightly sealed, light- and oxygen-resistant containers. Store in a cool place.■2S (*USP29*)

Change to read:

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—
Spectral range: 300 to 700 nm.
Solution—Prepare as directed for the *Test solution* in the test for *Content of total carotenoids.*
Ratio: A_{446}/A_{474}, between ~~1.09 and 1.11~~

■1.10 and 1.14.■2S (*USP29*)
B: The retention time for 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 *Content of lutein.*

Change to read:

Zeaxanthin and other related compounds—

■[NOTE—Use low-actinic glassware.]■2S (*USP29*)
Solvent, Mobile phase, Standard solution, Test solution, and *Chromatographic system*—Proceed as directed under *Content of lutein*.
Procedure—Inject a volume ~~(about 10 µL)~~

■(about 25 µL)■2S (*USP29*)
of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses.

■The peak area of zeaxanthin is not more than 9.0% of the total detected area of peaks in the chromatogram of the *Test solution.*■2S (*USP29*)
Calculate the percentage of zeaxanthin in the portion of Lutein taken by the formula:

$$T(r_i/r_s)$$

in which T is the content, in percentage, of total carotenoids as determined in the test for *Content of total carotenoids;* r_i is the individual peak response of zeaxanthin; and r_s is the sum of the responses of all the peaks: not more than ~~8.0%~~

■8.5%■2S (*USP29*)
of zeaxanthin is found. Calculate the percentage of other related compounds in the portion of Lutein taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the individual peak response of any other peak in the chromatogram (excluding zeaxanthin and lutein); and r_s is the sum of the responses of all the peaks: not more than 0.1% of any single other impurity is found.

Change to read:

Content of lutein—

■[NOTE—Use low-actinic glassware.]■2S (*USP29*)
Solvent: a mixture of hexanes, acetone, toluene, and dehydrated alcohol (10 : 7 : 7 : 6).
Mobile phase—Prepare a filtered and degassed mixture of ~~hexane and ethyl acetate (75 : 25)~~

■hexanes, methylene chloride, methanol, and diisopropylethylamine (74.6 : 24.9 : 0.4 : 0.1).■2S (*USP29*)
Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

In-Process Revision

Standard solution—Dissolve a suitable quantity of USP Lutein RS in *Mobile phase* to obtain a solution containing about ~~150 µg~~

■20 µg of lutein■2S (*USP29*)
per mL.
Test solution—Transfer about ~~1 mL~~

■0.1 mL■2S (*USP29*)
of *Test stock solution* from the test for *Content of total carotenoids,* and evaporate under a stream of nitrogen to dryness. Add 1 mL of *Mobile phase,* and sonicate to dissolve.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 446-nm detector and a 4.6-mm × 25-cm column that contains ~~3-µm packing L3~~

■5-µm packing L10.■2S (*USP29*)
The flow rate is about ~~1.5 mL~~

■1.0 mL■2S (*USP29*)
per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about ~~1.05~~

■1.10■2S (*USP29*)
for zeaxanthin and 1.0 for lutein; the resolution, *R*, between lutein and zeaxanthin is not less than ~~1.0~~

■2.0;■2S (*USP29*)
the tailing factor is not more than ~~2~~

■1.5;■2S (*USP29*)
and the relative standard deviation for replicate injections is not more than 2.0%.
Procedure—Inject a volume ~~(about 10 µL)~~

■(about 25 µL)■2S (*USP29*)
of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak

■area■2S (*USP29*)
responses.

■The peak area of lutein is not less than 85.0% of the total detected area of peaks in the chromatogram.■2S (*USP29*)
Calculate the percentage of Lutein taken by the formula:

$$T(r_i / r_s)$$

in which T is the content, in percentage, of total carotenoids as determined in the test for *Content of total carotenoids;* r_i is the individual peak response of lutein in the *Test solution;* and r_s is the sum of the responses of all the peaks: not less than ~~75.0%~~

■74.0%■2S (*USP29*)
of lutein is found.

Change to read:

Content of total carotenoids—

■[NOTE—Use low-actinic glassware.]■2S (*USP29*)
Solvent: a mixture of hexanes, acetone, toluene, and dehydrated alcohol (10 : 7 : 7 : 6).
Test stock solution—Transfer about ~~15 mg~~

■30 mg■2S (*USP29*)
of Lutein to a 100-mL volumetric flask, and dissolve in and dilute with *Solvent* to volume.

Test solution—Quantitatively dilute the *Test stock solution* (1 in 100) with dehydrated alcohol to obtain a solution having a final concentration of about ~~1.5 µg per mL.~~

■3.0 µg per mL.■2S (*USP29*)
Procedure—Determine the absorbance of the *Test solution* at the wavelength of maximum absorbance at about 446 nm, with a suitable spectrophotometer, using dehydrated alcohol as a blank. Calculate the percentage of total carotenoids as lutein ($C_{40}H_{56}O_2$) by the formula:

~~$$1000A / 255W,$$~~

■$$10{,}000A / 2550W$$■2S (*USP29*)

in which A is the absorbance of the *Test solution; W* is the weight, in g, of Lutein taken to prepare the *Test stock solution;* and 2550 is the absorptivity of the ~~pure lutein~~

■lutein in alcohol.■2S (*USP29*)

BRIEFING

Lutein Preparation, *USP 28* page 2112—See briefing under *Lutein*.

(DSN: L. Evans) RTS—42699-2

Change to read:

» Lutein Preparation is a combination of lutein with one or more inert substances. It may be in a solid or a liquid form. It contains not less than 95.0 percent and not more than 120.0 percent of the labeled amount of ~~total carotenoids~~

■lutein,■2S (*USP29*)
calculated as ~~lutein~~

■■2S (*USP29*)
$C_{40}H_{56}O_2$ on the anhydrous basis. The lutein content of total carotenoids is not less than ~~93.5~~

■85.0■2S (*USP29*)
percent, and the zeaxanthin content is not more than ~~10.0~~

■9.0■2S (*USP29*)
percent.

In-Process Revision

Change to read:

Packaging and storage—~~Preserve in tight, light-resistant containers, in a cold place.~~

■Preserve in tightly sealed, light- and oxygen-resistant containers. Store in a cool place.■2S (*USP29*)

Change to read:

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—
Spectral range: 300 to 700 nm.
Solution—Prepare as directed for the *Test solution* in the test for *Content of total carotenoids.*
Ratio: A_{446}/A_{474}, between ~~1.09 and 1.11~~

■1.10 and 1.14.■2S (*USP29*)
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 *Content of lutein.*

Change to read:

Zeaxanthin and other related compounds—
Solvent, Mobile phase, Standard solution, Test solution, and *Chromatographic system*—Proceed as directed under *Content of lutein*.
Procedure—Inject a volume ~~(about 10 µL)~~

■(about 25 µL)■2S (*USP29*)
of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of zeaxanthin and other related compounds relative to total carotenoids in the Preparation taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the individual peak response of zeaxanthin

■or any other peak in the chromatogram (excluding lutein),■2S (*USP29*)
and r_s is the sum of the responses of all the peaks: ~~Calculate the percentage of other related compounds relative to total carotenoids in the Preparation taken by the formula:~~

~~$100(r_i/r_s)$~~

~~in which r_i is the individual peak response of any other peak in the chromatogram (excluding zeaxanthin and lutein), and r_s is the sum of the responses of all the peaks.~~

■not more than 9.0% of zeaxanthin is found;■2S (*USP29*)
not more than 0.1% of any other ~~impurity~~

■related compound■2S (*USP29*)
is found;

■and the total related compounds (including zeaxanthin) found are not less than 15.0%.■2S (*USP29*)

Change to read:

Content of lutein—
Solvent: a mixture of hexanes, acetone, toluene, and dehydrated alcohol (10 : 7 : 7 : 6).
Mobile phase—Prepare a filtered and degassed mixture of ~~hexane and ethyl acetate (75 : 25).~~

■hexanes, methylene chloride, methanol, and diisopropylethylamine (74.6 : 24.9 : 0.4 : 0.1).■2S (*USP29*)
Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard solution—Dissolve a suitable quantity of USP Lutein RS in *Mobile phase* to obtain a solution containing about ~~150 µg~~

■20 µg of lutein■2S (*USP29*)
per mL.
Test solution—Transfer ~~1.0 mL~~

■0.1 mL■2S (*USP29*)
of *Test stock solution 1,* or ~~1.0~~

■0.1■2S (*USP29*)
mL of *Test stock solution 2,* or ~~2.0~~

■0.1■2S (*USP29*)
mL of *Test stock solution 3* from the test for *Content of total carotenoids* into a suitable vial. Evaporate the solvent to dryness under a stream of nitrogen. Add about 1.0 mL of *Mobile phase,* and sonicate to dissolve.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 446-nm detector and a 4.6-mm × 25-cm column that contains ~~3-µm packing L7~~

■5-µm packing L10.■2S (*USP29*)
The flow rate is about ~~1.5~~

■1.0■2S (*USP29*)
mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about ~~1.05~~

■1.10■2S (*USP29*)
for zeaxanthin, and 1.0 for lutein; the resolution, *R,* between lutein and zeaxanthin is not less than ~~1.0~~

■2.0;■2S (*USP29*)
the tailing factor is not more than ~~2~~

■1.5;■2S (*USP29*)
and the relative standard deviation for replicate injections is not more than 2.0%.
Procedure—Inject a volume ~~(about 10 µL)~~

■(about 25 µL)■2S (*USP29*)
of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of lutein relative to total carotenoids in the Preparation taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the individual peak response of lutein, and r_s is the sum of the responses of all the peaks: not less than ~~93.5%~~

■85.0%■2S (*USP29*)
of lutein is found.

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■Calculate the amount of lutein in the Preparation using the formula:

$$T(r_i / r_s)$$

in which T is the content, in percentage, of total carotenoids as determined in the test for *Content of total carotenoids;* r_i is the individual peak response of lutein in the *Test solution;* and r_s is the sum of the responses of all the peaks.■2S (*USP29*)

Change to read:

Content of total carotenoids—

Solvent: a mixture of hexanes, acetone, toluene, and dehydrated alcohol (10 : 7 : 7 : 6).

Test stock solution 1 (for solid lutein preparations labeled as containing gelatin)— ~~Transfer the amount of Preparation, equivalent to about 4.5 mg of lutein, to a 100-mL flask. Add about 20 mL of warm water, about 60 Unitsof a bacterial alkaline protease preparation, and 1 mg of bromelain. Insert the stopper into the flask, and sonicate for 30 minutes with occasional swirling. Cool to room temperature, and add 30.0 mL of methylene chloride. Shake the flask for 1 minute, and place in the dark for 30 minutes to allow separation of the layers. Transfer about 10 mL of the red lower layer to a test tube containing 2 to 3 g of anhydrous sodium sulfate. Insert the stopper into the tube, and shake gently.~~

■Transfer the amount of Preparation, equivalent to about 3.5 mg of lutein, to a 50-mL centrifuge tube. Add about 15 mL of warm water, 60 units of bacterial alkaline protease preparation, and 1 mg of bromelain. Cap and sonicate for 20 minutes with occasional swirling. Cool to room temperature, and add 20.0 mL of methylene chloride. Shake for 1 minute, and centrifuge for 5 minutes at 2000 rpm. Remove the upper aqueous phase, and add 2 to 3 g of anhydrous sodium sulfate to the remaining red layer.■2S (*USP29*)

Test stock solution 2 (for other solid lutein preparations)— ~~Transfer the amount of Preparation, equivalent to about 4.5 mg of lutein, to a 100-mL flask. Add about 20 mL of warm water, insert the stopper into the flask, and sonicate for 30 minutes with occasional swirling. Cool to room temperature, and add 30.0 mL of methylene chloride. Shake the flask for 1 minute, and place in the dark for 30 minutes to allow separation of the layers. Transfer about 10 mL of the red lower layer to a test tube containing 2 to 3 g of anhydrous sodium sulfate. Insert the stopper into the tube, and shake gently.~~

■Transfer the amount of Preparation, equivalent to about 1.5 mg of lutein, to a 50-mL centrifuge tube. Add about 15 mL of warm water, cap, and sonicate for 30 minutes with occasional swirling. Cool to room temperature, and add 30.0 mL of ethyl acetate and 2 to 3 g of sodium chloride. Shake for 1 minute, and centrifuge for 5 minutes at 2000 rpm. The upper orange-red layer is *Test stock solution 2.*■2S (*USP29*)

Test stock solution 3 (for liquid lutein suspensions in oil)—Transfer an accurately weighed amount of Preparation, equivalent to about ~~6 mg~~

■20 mg■2S (*USP29*)
of lutein, to a 100-mL volumetric flask, and dilute with *Solvent* to volume. Add a magnetic bar, and stir for 30 minutes.

Test solution—Transfer 1.0 mL of *Test stock solution 1,* or 1.0 mL of *Test stock solution 2,* or ~~2~~

■1.0■2S (*USP29*)
mL of *Test stock solution 3* into a 100-mL volumetric flask, and dilute with dehydrated alcohol to volume.

Procedure—Determine the absorbance of the *Test solution* at the wavelength of maximum absorbance at about 446 nm, with a suitable spectrophotometer, using dehydrated alcohol as a blank. Calculate the percentage of total carotenoids as lutein ($C_{40}H_{56}O_2$) in the Preparation by the formula:

$$~~100VDA / 225W,~~$$

$$■VDA / 2550W■2S\ (USP29)$$

in which V is the volume of organic solvent (30.0 mL for *Test stock solution 1,* ~~30.0 mL~~

■100.0 mL■2S (*USP29*)
for *Test stock solution 2,* and 100.0 mL for *Test stock solution 3*) used in preparing the *Test stock solution; D* is the dilution factor used in preparing the *Test solution; A* is the absorbance of the *Test solution; W* is the weight, in ~~mg~~

■g,■2S (*USP29*)
of Preparation taken to prepare the *Test stock solution;* and ~~255~~

■2550■2S (*USP29*)
is the absorptivity of the ~~pure lutein~~

■lutein in alcohol.■2S (*USP29*)

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MONOGRAPHS (NF)

BRIEFING

Amino Methacrylate Copolymer. Because there is no existing *NF* monograph for this excipient, a new monograph, based on submitted data, is being proposed. The procedure in *Test 1* under *Limit of monomers* is based on analysis performed with the Nucleosil C18 brand of L1 columns, and *Test 2* is based on analysis performed with the Nucleosil NH2 brand of L8 columns. The typical retention times in *Test 1* for methyl methacrylate and butyl methacrylate are about 1.8 minutes and 8.4 minutes, respectively. The typical retention time in *Test 2* is about 2.0 minutes for (2-dimethylaminoethyl) methacrylate.

(EMC: C. Sheehan; NL: W. Paul; PSD: C. Okeke) RTS—39405-1; 40243-1

Add the following:

■Amino Methacrylate Copolymer

» Amino Methacrylate Copolymer is a fully polymerized copolymer of (2-dimethylaminoethyl) methacrylate, butyl methacrylate, and methyl methacrylate. It contains not less than 20.8 percent and not more than 25.5 percent dimethylaminoethyl groups ($C_4H_{10}N$), calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at a temperature not exceeding 25°.

USP Reference standards ⟨11⟩—*USP Amino Methacrylate Copolymer RS.*

Color of solution—The absorbance of the *Test solution* prepared in the test under *Viscosity,* determined in a 1-cm cell at 420 nm in a suitable spectrophotometer, is not greater than 0.300. Use water as the blank.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Pour 1 mL of the *Test solution* prepared in the test under *Viscosity* onto a glass plate and allow the solvent to evaporate: a clear, colorless film results.

Viscosity ⟨911⟩—

Test solution—Dissolve 12.5 g in a mixture of 35.0 g of acetone and 52.5 g of isopropyl alcohol. [NOTE—Reserve a portion of this solution for the *Color of solution* test.]

Procedure—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, 9.074 cm in height, and has a shaft 0.40 cm in diameter. Transfer 16 mL of the *Test solution* into the measuring cylinder, and adjust the temperature of the solution 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 between 3 and 6 centipoises.

Loss on drying ⟨731⟩—Dry it at 110° for 3 hours: it loses not more than 2.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Limit of monomers—

TEST 1, LIMIT OF BUTYL METHACRYLATE AND METHYL METHACRYLATE—

pH 2.0 Phosphate buffer (0.0625 M)—Prepare an aqueous solution containing 8.9 g of anhydrous dibasic sodium phosphate and 8.5 g of monobasic potassium phosphate per L. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase—Prepare a mixture of methanol and *pH 2.0 Phosphate buffer (0.0625 M)* (55 : 45).

Standard solution—Prepare a solution in acetonitrile having a concentration of about 1000 µg per mL each of butyl methacrylate and methyl methacrylate. Dilute 1.0 mL of the solution to 250.0 mL with water, and mix.

Test solution—Dissolve about 1.0 g of Amino Methacrylate Copolymer, accurately weighed, in *pH 2.0 Phosphate buffer (0.0625 M),* and dilute with *pH 2.0 Phosphate buffer (0.0625 M)* to 50.0 mL, and mix.

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 2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between butyl methacrylate and methyl methacrylate is not less than 10; 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 responses for the major peaks. Calculate the quantity, in µg, of each monomer in the portion of Amino Methacrylate Copolymer taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of each monomer in the *Standard solution;* and r_U and r_S are the peak responses of each monomer obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of each monomer is found.

TEST 2, LIMIT OF 2-DIMETHYLAMINOETHYL METHACRYLATE—

Potassium monobasic phosphate solution (0.025M)—Prepare an aqueous solution containing 3.4 g of monobasic potassium phosphate per L.

Mobile phase—Prepare a mixture of *Potassium monobasic phosphate solution (0.025M)* and tetrahydrofuran (75 : 25).

Standard solution—Prepare a solution in tetrahydrofuran having a concentration of about 200 µg per mL of (2-dimethylaminoethyl) methacrylate. Dilute 2.0 mL of the solution to 50.0 mL with tetrahydrofuran, and mix.

Test solution—Dissolve about 1.0 g of Amino Methacrylate Copolymer, accurately weighed, in tetrahydrofuran, dilute with tetrahydrofuran to 50.0 mL, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 12-cm column that contains packing L8. The flow rate is about 2 mL per minute. 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 the *Test solution* into the chromatograph, record the chromatograms, and measure the

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response for the major peak. Calculate the quantity, in µg, of (2-dimethylaminoethyl) methacrylate in the portion of Amino Methacrylate Copolymer taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of the monomer in the *Standard solution;* and r_U and r_S are the peak responses of (2-dimethylaminoethyl) methacrylate obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% is found.

Assay—Dissolve 0.20 g in a mixture of 4 mL of water and 96 mL of glacial acetic acid, and mix. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). One mL of 0.1 N perchloric acid is equivalent to 7.21 mg of dimethylaminoethyl groups ($C_4H_{10}N$).■2S (*NF24*)

■The indicated viscosity may be in the form of a range encompassing 80.0% to 120.0% of the nominal viscosity, where the solution concentration is 1% (w/w); and 75.0% to 140.0% of the nominal viscosity, where the solution concentration is 2% (w/w).■2S (*NF24*)

Change to read:

Viscosity ⟨911⟩—Determine the viscosity in a water solution at the concentration stated on the label. Using undried Carboxymethylcellulose Sodium 12, weigh accurately the amount which, on the dried basis, will provide 200 g of solution of the stated concentration. Add the substance in small amounts to about 180 mL of stirred water contained in a tared, wide-mouth bottle, continue stirring rapidly until the powder is well wetted, add sufficient water to make the mixture weigh 200 g, and allow to stand, with occasional stirring, until solution is complete. Adjust the temperature to 25 ± 0.2°, and determine the viscosity, using a rotational type of viscosimeter, making certain that the system reaches equilibrium before taking the final reading. The viscosity of solutions of 2% concentration is not less than 80.0% and not more than 120.0% of that stated on the label; the viscosity of solutions of 1% concentration is not less than 75.0% and not more than 140.0% of that stated on the label

■or it is between the maximum and minimum values, where stated as a range of viscosities.■2S (*NF24*)

BRIEFING

Carboxymethylcellulose Sodium 12, *NF 23* page 2978. It is proposed to revise the *Labeling* and *Viscosity* sections to allow viscosity to be stated as a range of viscosities. The proposed range corresponds to the requirements under *Viscosity,* when it is stated as a single value.

(EMC: J. Lane) RTS—42626-1

Change to read:

Labeling—Label it to indicate the

■nominal■2S (*NF24*)
viscosity in solutions of stated concentrations of either 1% (w/w) or 2% (w/w).

BRIEFING

Microcrystalline Cellulose, *NF 23* page 2982 and page 3353 of the *First Supplement.* It is proposed to revise the *Labeling* section and the *Particle size distribution* section to allow for other procedures to be employed, such as laser diffraction techniques.

(EMC: J. Lane) RTS—42509-1; 42598-1; 42628-1; 42630-1

Change to read:

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, proceed as directed under ~~*Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩~~;

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■*Particle size distribution*. The labeling indicates with which technique the particle size distribution was determined if a technique other than analytical sieving was used; and■2S (*NF24*)
the labeling indicates the d_{10}, d_{50}, and d_{90} values ~~(see *Powder Fineness* ⟨811⟩.)~~

■■2S (*NF24*)
and the range for each.

Change to read:

~~**Particle size distribution estimation by analytical sieving** ⟨786⟩~~

■**Particle size distribution**■2S (*NF24*)
—[NOTE—In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.] Where the labeling states the particle size distribution, determine the particle size distribution as directed in ~~the chapter~~

■*Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩ or by a suitable validated procedure.■2S (*NF24*)

BRIEFING

Cyclomethicone, *NF 23* page 2994. It is proposed to add a reference to *Spectrophotometric Identification Tests* ⟨197⟩ in the *Identification* section.

(PA4: E. Gonikberg) RTS—42574-1

Change to read:

Identification—

■Proceed as directed under ⟨197S⟩, except to use neat liquids.■2S (*NF24*)
The IR absorption spectrum, determined in a 0.1-mm cell, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cyclomethicone 4 RS, USP Cyclomethicone 5 RS, or USP Cyclomethicone 6 RS.

BRIEFING

Dibutyl Sebacate, *NF 23* page 2997. On the basis of comments received, it is proposed to revise the acceptance criteria for the *Saponification value*.

(EMC: D. Bempong) RTS—42560-1

Change to read:

Saponification value ⟨401⟩: between ~~352 and 357.~~

■352 and 360.■2S (*NF24*)

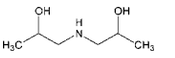
BRIEFING

Diisopropanolamine. It is proposed to reinstate this excipient monograph, which was omitted in *NF XVIII.*

(EMC: K. Russo; PSD: C. Okeke) RTS—42519-1; 42519-2

Add the following:

■Diisopropanolamine



$C_6H_{15}NO_2$ 133.19

2-Propanol, 1,1′-iminobis-.

1,1′-Iminodi-2-propanol [*110-97-4*].

» Diisopropanolamine is a mixture of isopropanolamines, consisting largely of diisopropanolamine. It contains not less than 98.0 percent and not more than 102.0 percent of isopropanolamines, calculated on the anhydrous basis as $NH(C_3H_6OH)_2$.

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Packaging and storage—Preserve in tight, light-resistant containers. No specific storage conditions required.

Identification—The infrared absorption spectrum of a thin film exhibits regions of absorption between 2.8 µm and 4.0 µm, between 6.7 µm and 7.1 µm, and between 8.5 µm and 9.4 µm; and several characteristic peaks, the most pronounced being at about 7.3 µm, 7.5 µm, 8.3 µm, 9.6 µm, 10.4 µm, and 10.7 µm.

Water, *Method I* ⟨921⟩**:** not more than 0.50%, a mixture of 5.0 mL of glacial acetic acid and 25 mL of methanol being used as the solvent.

Triisopropanolamine—

Mixed indicator—Dissolve about 150 mg of methyl orange and about 80 mg of xylene cyanole FF in water, and dilute with water to 100 mL.

Procedure—Add 100 mL of methanol and 6 to 8 drops of *Mixed indicator* in a glass-stoppered, 500-mL conical flask, and neutralize with 0.1 N alcoholic sulfuric acid or 0.1 N alcoholic potassium hydroxide. The neutral solution is amber when viewed by transmitted light and is red-brown when viewed by reflected light. Add about 20 g of Diisopropanolamine, accurately weighed. Cautiously add 75 mL of acetic anhydride, and swirl to dissolve. Allow to stand at room temperature for 30 minutes. Cool to room temperature, if necessary. Titrate with 0.5 N alcoholic sulfuric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N alcoholic sulfuric acid is equivalent to 95.7 mg of triisopropanolamine: the limit is 1.0% by weight.

Assay—Transfer about 2 g mg of Diisopropanolamine, accurately weighed, to a 250-mL conical flask, add 50 mL of water and bromocresol green TS, and titrate with 0.5 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.5 N hydrochloric acid is equivalent to 66.60 mg of isopropanolamines, expressed as $NH(C_3H_6OH)_{2\cdot}$■2S *(NF24)*

BRIEFING

Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion. Because there is no existing *NF* monograph for this article, a new monograph, based on submitted data, is being proposed. The liquid chromatographic procedure in the test for *Limit of monomers* is based on analyses performed with a Nucleosil C18 brand of L1 column. Typical retention times for ethyl acrylate and methyl methacrylate are about 6.0 and 6.8 minutes, respectively.

(EMC: C. Sheehan; NL: W. Paul; AMB: R. Tirumalai; PSD: C. Okeke) RTS—41750-1

Add the following:

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion

[*9010-88-2*].

» Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion is an aqueous dispersion of a copolymer of ethyl acrylate and methyl methacrylate having an average molecular weight of about 800,000. It may contain suitable emulsifying agents.

Packaging and storage—Preserve in well-closed containers. Store between 5° and 25°, with excursions permitted up to 30°. Do not freeze.

Labeling—Label it to indicate the name and quantity of any added emulsifiers.

USP Reference standards ⟨11⟩**—***USP Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion RS.*

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Identification, *Infrared Absorption* ⟨197K⟩.

Viscosity ⟨911⟩—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 Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion, pipet 16 mL into the measuring cylinder, and adjust the temperature of the Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion and the adapter to $20 \pm 0.1^{\circ}$. 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 50 centipoises.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g and total yeast and mold count does not exceed 100 cfu per g.

pH ⟨791⟩**:** between 5.5 and 8.6.

Loss on drying ⟨731⟩—Dry it at 110° for 3 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) to avoid loss of material, evaporate the Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion to dryness prior to ignition: not more than 0.4% residue is obtained, calculated on the undried basis.

Limit of monomers—

Sodium perchlorate solution—Dissolve 3.5 g of sodium perchlorate in 100 mL of water.

pH 2.0 Phosphoric acid—Dilute phosphoric acid with water to obtain a solution having a pH of 2.0.

Mobile phase—Prepare a mixture of *pH 2.0 Phosphoric acid* and methanol (80 : 20), filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution in tetrahydrofuran having a concentration of about 2 µg per mL each of ethyl acrylate and methyl methacrylate. To 10.0 mL of this solution add 5.0 mL of a *Sodium perchlorate solution,* and mix. Dilute 5.0 mL of the mixture to 10.0 mL with water, and mix.

Test stock solution—Dissolve 1.0 g of Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion with tetrahydrofuran, and dilute with the same solvent to 50 mL.

Test solution—To 5.0 mL of *Sodium perchlorate solution* add 10.0 mL of the *Test stock solution*, dropwise, while stirring continuously. Centrifuge and filter the clear supernatant. Dilute 5.0 mL of the clear supernatant with water to 10.0 mL, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 200-nm detector and a 4.6- × 120-mm 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 resolution, *R,* between ethyl acrylate and methyl methacrylate peaks is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for each analyte.

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 quantity, in µg, of each monomer in the portion of Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion taken by the formula:

$$10C(r_U / r_S)$$

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in which C is the concentration, in µg per mL, of the monomer in the *Standard solution;* and r_U and r_S are the peak responses for the monomer obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.01% of total monomers is found.

Coagulum content—Accurately weigh a stainless steel sieve having 125-µm openings, and filter 100 g of Ethyl Acrylate and Methyl Methacrylate Copolymer 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%).■2S *(NF24)*

BRIEFING

Lactitol, *NF 23* page 3023. It is proposed to correct the calculations in the test for *Related compounds*.

(PA4: E. Gonikberg) RTS—42599-1

Change to read:

Related compounds—

Standard solution—Dissolve an accurately weighed quantity of USP Lactitol RS in water to obtain a solution having a known concentration of about 0.3 mg per mL.

Chromatographic system—Proceed as directed in the *Assay*, except to chromatograph the *Standard solution* instead of the *Standard preparation.*

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 responses. The relative retention times are about 0.53 for lactose, 0.58 for glucose, 0.67 for galactose, 0.72 for lactulitol, 1.0 for lactitol, 1.55 for galactitol, and 1.68 for sorbitol. Calculate the percentages of galactitol, sorbitol, lactulitol, lactose, glucose, and galactose in the portion of Lactitol taken by the formula:

~~$1000(C/W)(r_U/r_S)$,~~

■$100(CV/W)(r_U/r_S)$■2S *(NF24)*

in which C is the concentration, in mg per mL, of USP Lactitol RS in the *Standard solution*;

■V is the volume, in mL, of the *Test solution;*■2S *(NF24)*
W is the weight, in mg, of Lactitol in the *Test solution;* r_U is the peak response of the relevant related compound, if observed, obtained from the *Test solution;* and r_S is the lactitol peak response obtained from the *Standard solution*. The total of the percentages of all related compounds is not more than 1.5%.

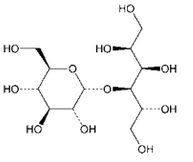
BRIEFING

Maltitol. Because there is no existing *NF* monograph for this article, the following new monograph is proposed based on a manufacturer's tests and acceptance criteria. The liquid chromatographic procedure in the *Assay* is based on analysis performed using a Biorad Aminex Fast Carbohydrate brand of L34 column; maltitol peak elutes at approximately 8.7 minutes.

(EMC: C. Sheehan; NL: W. Paul; PSD: C. Okeke; AMB: R. Tirumalai) RTS— 41979-1

Add the following:

■Maltitol



$C_{12}H_{24}O_{11}$ 344.31

D-Glucopyranosyl-D-glucitol [*585-88-6*].

» Maltitol contains not less than 92.0 percent and not more than 100.5 percent of D-maltitol, calculated on the anhydrous basis. The amounts of total sugars, other polyhydric alcohols, and any polyol

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anhydrides, if detected, are not included in the requirements or in the calculated amount under *Other Impurities* in *General Notices and Requirements.*

Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

USP Reference standards ⟨11⟩—*USP Maltitol RS.*

Identification—

A: Dissolve 1 g of Maltitol 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 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.*

Microbial limits ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 1000 cfu per g and the total combined molds and yeasts count is not more than 100 cfu per g.

Conductivity—Dissolve 20.0 g of Maltitol in water, and dilute with the same solvent to 100.0 mL. Using an appropriate conductivity meter, choose a conductivity cell that is appropriate for the properties and conductivity of the solution to be examined. Use a certified reference material[1], for example a solution of potassium chloride, that is appropriate for the measurement. The conductivity value of the certified reference material should be near the expected conductivity value of the solution to be examined. After calibrating the apparatus with a certified reference material solution, rinse the conductivity cell several times with water and at least twice with the aqueous solution to be examined. Measure the conductivity of the solution at a temperature of 20°, while gently stirring with a magnetic stirrer: the conductivity is not more than 20 μS per cm.

Water, *Method I* ⟨921⟩**:** not more than 1.0%.

Reducing sugars—Dissolve 3.3 g of Maltitol in 3 mL of water with the aid of gentle heat. 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*.

Limit of nickel—not more than 1 μg per g calculated on the anhydrous basis is found. Proceed as directed in the test for *Limit of nickel* under *Sorbitol.*

Assay—

Mobile phase—Use degassed water.

Standard preparation—Dissolve accurately weighed quantities of USP Maltitol RS and sorbitol in water, to obtain a solution having known concentrations of about 10 mg per g and 1.6 mg per g, respectively.

[1] Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Standards 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.

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Resolution solution—Dissolve accurately weighed quantities of USP Maltitol RS and sorbitol in water to obtain a solution having known concentrations of about 4.8 mg of each per g.

Assay preparation—Dissolve about 0.20 g of Maltitol, 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 chromatographic system is equipped with a refractive index detector maintained at a constant temperature of about 35°, and a 7.8-mm × 10-cm column that contains packing L34 (see *Chromatography* ⟨621⟩). The column temperature is maintained at about 60°, controlled to within ±2°, and the flow rate is about 0.5 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.48 for maltitol, and 1.0 for sorbitol; the resolution, *R*, between maltitol and sorbitol 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 10 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage, on the anhydrous basis, of $C_{12}H_{24}O_{11}$, in the portion of Maltitol 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 USP Maltitol RS in the *Standard preparation;* C_U is the concentration, in mg per g, of Maltitol 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.* ■2S (*NF24*)

BRIEFING

Nitrogen, *NF 23* page 3041, page 3359 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 708 of *PF* 31(3) [May–June 2005]—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-8

Change to read:

» Nitrogen contains not less than 99.0 percent, ~~by volume~~

■volume/volume,■2S (*NF24*)
of N_2.

Change to read:

Packaging and storage—~~Preserve in cylinders.~~

■Preserve in black cylinders. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S (*NF24*)

Change to read:

Assay—Introduce a specimen of Nitrogen into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 3 m in length and 4 mm in inside diameter and is packed with a molecular sieve prepared from a synthetic alkali-metal aluminosilicate capable of absorbing molecules having diameters of up to 0.5 nm, which permit complete separation of oxygen from nitrogen. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •~~the USP Oxygen–Helium RS,~~•.

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■the USP Nitrogen RS,■2S *(NF24)* and is equivalent to not more than 1.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•3 indicating not less than 99.0%, by volume, of N_2.

■•(Postponed indefinitely)•3 ■2S *(NF24)*

BRIEFING

Nitrogen 97 Percent, *NF 23* page 3041, page 3359 of the *First Supplement,* and the *Third Interim Revision Announcement (Notice of Postponement)* on page 708 of *PF* 31(3) [May–June 2005]—See briefing under *Medical Air.*

(AER: K. Zaidi) RTS—42651-9

Change to read:

» Nitrogen 97 Percent is Nitrogen produced from air by physical separation methods. It contains not less than 97.0 percent, ~~by volume~~

■volume/volume,■2S *(NF24)* of N_2.

Change to read:

Packaging and storage—~~Preserve in cylinders or in a low-pressure collecting tank.~~

■Preserve in black cylinders or a black low-pressure collecting tank. Containers and connections are to be specific to the application and must be controlled in such a fashion that there are sufficient change controls to prevent the connection of the incorrect gas to the system (such as those suggested in CGA Standard CGA V-1-2003).■2S *(NF24)*

Change to read:

Assay—Proceed as directed in the *Assay* under *Nitrogen.* The peak response produced by the assay specimen exhibits a retention time corresponding to that produced by •~~the USP Oxygen–Helium RS,•3~~

■the USP Nitrogen 97 Percent RS■2S *(NF24)* and is equivalent to not more than 3.0% of oxygen when compared to the peak response of the •USP Oxygen–Helium RS,•3 indicating not less than 97.0%, by volume, of N_2.

■•(Postponed indefinitely)•3 ■2S *(NF24)*

BRIEFING

Sodium Sulfite, *NF 23* page 3081. On the basis of comments received, it is proposed to revise *Identification* test *A.*

(EMC: E. Gonikberg) RTS—42523-1

Change to read:

Identification—

A: Dissolve 5 g of Sodium Sulfite in 100 mL of water. ~~the pH of the solution is between 8.0 and 10.0.~~

■■2S *(NF24)*

[NOTE—Reserve portions of the solution so obtained for use in *Identification* test *B* and in the test for *Color and clarity of solution.*]

■Add a drop of phenolphthalein TS: a pink color is produced.■2S *(NF24)*

B: To 5 mL of the solution from *Identification* test *A,* add 0.5 mL of iodine TS: the solution is colorless and it meets the requirements of the barium chloride test for *Sulfate* ⟨191⟩.

C: It meets the requirements of the pyroantimonate precipitate test for *Sodium* ⟨191⟩.

BRIEFING

Sucralose, *NF 23* page 3093. This proposed revision clarifies the test for *Limit of hydrolysis products.*

(EMC: R. Ravichandran) RTS—42609-1

Change to read:

Limit of hydrolysis products—

■[NOTE—This test does not require a developing solvent.]■2S *(NF24)*

Adsorbent: 0.25-mm layer of chromatographic silica gel.

Spray reagent—Dissolve about 1.23 g of *p*-anisidine and 1.66 g of phthalic acid in 100 mL of methanol. Store the solution in the dark and refrigerate to prevent discoloration. Discard if the solution becomes discolored. *[Caution—p-Anisidine is toxic if inhaled or if absorbed through the skin.]*

Standard solution 1—Transfer about 10.0 g of mannitol to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

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Standard solution 2—Transfer about 40.0 mg of fructose and 10.0 g of mannitol to a 100-mL volumetric flask, dissolve in 25 mL of water, dilute with water to volume, and mix.

Test solution—Transfer about 2.5 g of Sucralose, accurately weighed, to a 10-mL volumetric flask, dissolve in about 5 mL of methanol, dilute with methanol to volume, and mix.

Application volume: 5-µL portions separately applied in 1-µL increments, allowing the plate to dry between applications.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Spray the plate with *Spray reagent,* and heat the plate at 100 ± 2° for 15 minutes. If the spot from *Standard solution 1* has darkened, repeat the test, heating for a shorter period of time. Immediately after heating, view the plate against a dark background: the color of the spot obtained from the *Test solution* is not more intense than that obtained from *Standard solution 2* (0.1%).

BRIEFING

Compressible Sugar, *NF 23* page 3095. On the basis of comments received, it is proposed to revise the test for *Loss on drying* to remove the lower limit of the acceptance criteria.

(EMC: D. Bempong) RTS—42559-1

Change to read:

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: ~~it loses between 0.25% and 1.0% of its weight.~~

■it loses not more than 1.0% of its weight.■2S (*NF24*)

BRIEFING

Confectioner's Sugar, *NF* 23 page 3095. It is proposed to revise the *Identification* test to remove a reference to the now deleted *Starch* monograph.

(EMC: D. Bempong) RTS—42616-1

Change to read:

Identification, Specific rotation, Chloride, Calcium, Sulfate, and Heavy metals—Transfer about 20 g, accurately weighed, to a 100-mL volumetric flask, add 80 mL of water, shake to dissolve the sucrose, then add water to volume, and mix. Separate the solubilized sucrose from the insoluble starch component by filtration until the filtrate is sparkling clear. Use the insoluble portion for the *Identification* test, and use the freshly prepared, clear filtrate for the other tests that follow.

Identification—A water slurry of the insoluble portion ~~responds to *Identification* test *B* under *Starch*~~

■is colored reddish-violet to deep blue by iodine TS.■2S (*NF24*)

Specific rotation ⟨781⟩: not less than +62.6°, determined on a portion of the filtrate, corresponding to not less than 95.0% of $C_{12}H_{22}O_{11}$, calculated on the dried basis.

Chloride ⟨221⟩—A 10-mL portion of the filtrate shows no more chloride than corresponds to 0.40 mL of 0.020 N hydrochloric acid (0.014%).

Calcium ⟨191⟩—To 5 mL of the filtrate add 5 mL of water and 1 mL of ammonium oxalate TS: the solution remains clear for not less than 1 minute.

Sulfate ⟨221⟩—A 25-mL portion of the filtrate shows no more sulfate than corresponds to 0.30 mL of 0.020 N sulfuric acid (0.006%).

Heavy metals ⟨231⟩—To 20 mL of the filtrate add 4 mL of water and 1 mL of 0.1 N hydrochloric acid: the limit is 5 ppm.

BRIEFING

Xylitol, *NF 23* page 3109. The proposed revison to the *Assay* specifies the use of USP Reference Standard materials in the *Internal standard solution* and in the *Standard preparation.* This proposal also affects the test for *Limit of other polyols.* Additional proposals in this test and in the *Assay* are intended to clarify the calculations.

(EMC: R. Ravichandran) RTS—42635-1

Change to read:

USP Reference standards ⟨11⟩—

■*USP L-Arabinitol RS. USP Erythritol RS. USP Galactitol RS. USP Mannitol RS. USP Sorbitol RS.*■2S (*NF24*)
USP Xylitol RS.

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Change to read:

Limit of other polyols—Using the chromatograms obtained in the *Assay,* separately calculate the percentage of each polyol in the portion of Xylitol taken by the formula:

~~$2500C/W\,(R_u/R_s),$~~

~~in which C is the concentration, in mg per mL, of the individual polyol in the *Standard preparation; W* is the weight, in mg, of Xylitol taken to prepare the *Assay preparation;* and R_u and R_s are the peak response ratios of the individual derivatized polyol to that of derivatized erythritol in the chromatograms of the solutions obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

■$100(C_S/C_U)(R_U/R_S)$

in which C_S and C_U are the concentrations, in mg per mL, of the individual polyol in the *Standard preparation* and *Assay preparation,* respectively; and R_U and R_S are the peak response ratios of the individual derivatized polyol to that of derivatized erythritol in the chromatograms of the solutions obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(NF24)*

The sum of the polyols found, calculated on the anhydrous basis, is not more than 2.0%.

Change to read:

Assay—

Internal standard solution—~~Transfer about 88 mg oferythritol to a 25-mL volumetric flask, dissolve in anddilute with water to volume, and mix.~~

■Dissolve an accurately weighed quantity of USP Erythritol RS in water to obtain a solution having a known concentration of about 3.5 mg per mL of erythritol.■2S *(NF24)*

Standard preparation—~~Transfer accurately weighed quantities of about 25 mg each of arabinitol, galactitol, mannitol, and sorbitolto a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 25-mL volumetric flask, add about 250 mg of USP Xylitol RS, accurately weighed, dilute with water to volume, and mix.~~

■Dissolve accurately weighed quantities of USP L-Arabinitol RS, USP Galactitol RS, USP Mannitol RS, USP Sorbitol RS, and USP Xylitol RS in water to obtain a solution having a known concentration of 0.05 mg per mL each of L-arabinitol, galactitol, sorbitol, and mannitol; and 10 mg per mL of xylitol.■2S *(NF24)*

Assay preparation—~~Transfer about 250 mg of Xylitol, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

■Dissolve an accurately weighed quantity of Xylitol in water to obtain a solution having a concentration of about 10 mg per mL.■2S *(NF24)*

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.25-mm × 30-m capillary column bonded with a 0.25-µm layer of phase G46. The carrier gas is helium flowing at a rate of about 1 mL per minute. The chromatograph is programmed to maintain the column temperature at 170° for 5 minutes, then to increase the temperature at a rate of 6° per minute to 215°, holding at that temperature for 8 minutes, then to increase the temperature at a rate of 10° per minute to 270°, which is held for 14 minutes. The temperature of the injection port is about 270°, and the detector temperature is about 280°. Chromatograph the solution obtained from the *Standard preparation* as directed for *Procedure*, and record the peak responses: the relative retention times corresponding to the derivatives of erythritol, L-arabinitol, xylitol, mannitol, galactitol, and sorbitol are about 0.47, 0.75, 0.81, 0.98, 0.99, and 1.0, respectively; and the relative standard deviation for the peak area ratios of xylitol to erythritol for replicate injections is not more than 1.5%.

Procedure—Transfer 1.0 mL each of the *Standard preparation* and the *Assay preparation* to separate round-bottom, 10-mL boiling flasks. To each flask, add 1.0 mL of *Internal standard solution*, and evaporate each of the mixtures under reduced pressure to dryness on a water bath at 60°, with the aid of a rotary evaporator. Add 1 mL of dehydrated alcohol, shake gently, and evaporate to dryness under the same conditions. Dissolve each residue in 1 mL of pyridine. Add 1 mL of acetic anhydride to each flask, cap each flask, and mix on a vortex mixer for 30 seconds. Store the closed flasks in an oven at 70° for 30 minutes. Separately inject equal volumes (about 1 µL) of the solutions obtained from 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 $C_5H_{12}O_5$ in the portion of Xylitol taken by the formula:

~~$2500(C/W)(R_u/R_s),$~~

~~in which C is the concentration, in mg per mL, of USP Xylitol RS in the *Standard preparation; W* is the weight, in mg, of Xylitol taken to prepare the *Assay preparation;* and R_u and R_s are the peak area ratios of derivatized xylitol to derivatized erythritol in the chromatograms of the solutions obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

■$100(C_S/C_U)(R_U/R_S)$

in which C_S and C_U are the concentrations, in mg per mL, of xylitol in the *Standard preparation* and the *Assay preparation,* respectively; and R_U and R_S are the peak area ratios of derivatized xylitol to derivatized erythritol in the chromatograms of the solutions obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(NF24)*

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**1**〉 **Injections,** *USP 28* page 2201 and page 504 of *PF* 31(2) [Mar.–Apr. 2005]. Based on a Stimuli article, "Report and Recommendations of the USP–FDA Advisory Panel on Simplification and Improvement of Injection Labeling" in *PF* 20(4) [July–Aug. 1994] and reports of medication errors from the USP/ISMP Medication Errors Reporting Program and the USP MEDMARX Program, the Parenteral Products—Industrial, Nomenclature and Labeling, and Safe Medication Use Expert Committees have agreed that the total strength and total volume should appear on a prominent area of the label for multiple-dose and single-dose injectable drug products. The implementation date for this proposal, *Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products,* will be thirty months from the date of publication in *Pharmacopeial Forum.*

(PPI: J. Kelly) RTS—42550-1; 42554-1

Change to read:

LABELS AND LABELING

Labeling

NOTE—See definitions of "label" and "labeling" under *Labeling* in the section *Preservation, Packaging, Storage, and Labeling* of the *General Notices and Requirements.*

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

■STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS

For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label followed in close proximity by strength per mL enclosed by parentheses. For containers less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL not mg/1 mL.

The following format would be acceptable for contents greater than 1 mL:

Total Strength/Total Volume: 500 mg/10 mL

Strength/mL: (50 mg/mL) or

Total Strength/Total Volume: 25,000 Units/5 mL

Strength/mL: (5,000 Units/mL)

The following format would be acceptable for contents less than 1 mL: 12.5 mg/0.625 mL

There are, however, some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be practical in preventing medication errors (e.g., insulin). An example is the use of lidocaine or other similar drugs used as a local anesthetic where the product is ordered and administered by percent (e.g., 1%, 2%) or a local anesthetic in combination with epinephrine which is expressed as a ratio (e.g., 1 : 100,000). In such cases, the total strength should be expressed (e.g., 1% (100 mg/10 mL). Dry solids, which need to be reconstituted, should follow the same format, with the exception that only the total strength of the drug is listed (not the strength/total volume or strength/mL).■2S (*USP29*)

(Official January 1, 2008)

~~Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition~~

~~(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (µg/L).~~

~~(b) The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per liter. This information must be contained in the "Precautions" section of the labeling of all large volume parenterals used in TPN therapy.~~

~~(c) The maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: "Contains no more than ___ µg of aluminum per liter." The immediate container label of all SVPs and PBPs that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ____ µg per liter." This maximum level of aluminum must be stated as the highest of the following:~~

~~(1) The highest level for the batches produced during the last 3 years;~~

~~(2) The highest level for the latest five batches, or~~

~~(3) The maximum historical level, but only until completion of production of the first five batches after January 26, 2001.~~

~~(d) The package insert for all LVPs, all SVPs, and PBPs used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state the following:~~

~~WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum.~~

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~~Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.~~

▲Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy

(a) The aluminum content of LVIs used in TPN therapy must not exceed 25 µg per L.

(b) The package insert of LVIs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVIs used in TPN therapy.

(c) If the maximum amount of aluminum in SVIs and PBPs is 25 µg per L or less, instead of stating the exact amount of aluminum that each may contain, as in paragraph (d), the immediate container label for SVIs and PBPs used in the preparation or in the administration of TPN injections (with exceptions as noted below) and injectable emulsions may state: "Contains no more than 25 µg/L of aluminum." If the SVI or PBP is a lyophilized powder, the immediate container label may state the following; if the SVI or PBP is a lyophilized powder used in the preparation of TPN injections and injectable emulsions, the immediate container label must state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L."

(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVIs and PBPs used in the preparation or the administration of TPN injections and injectable emulsions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum." This maximum amount of aluminum may be stated as the highest one of the following three levels:

1. The highest level for the batches produced during the last three years,
2. The highest level for the latest five batches, or
3. The maximum level in terms of historical levels, but only until completion of production of the first five batches after the effective date of July 26, 2004.

The package insert for all LVIs, SVIs, and PBPs used in the preparation or administration of TPN products must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling and must state the following: "WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain

aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products and of the lock-flush solutions used in their administration." ▲*USP29*

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

(Official October 1, 2005)

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. The contents of up to five 1- or 2-mL containers may be pooled for the measurement, provided that a

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separate dry syringe assembly is used for each container. The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: ''Warning'', ''Dilute Before Using'', ''Paralyzing Agent'', ''I.M. Use Only'', ''Chemotherapy'', etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

(Official October 1, 2005)

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

Change to read:

~~FOREIGN MATTER AND PARTICLES~~

▲FOREIGN AND PARTICULATE MATTER▲*USP29*

~~Foreign Matter~~

~~Every care should be exercised in the preparation of all products intended for injection to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents shows evidence of contamination with visible foreign material be rejected.~~

~~Particulate Matter~~

~~All large-volume Injections for single-dose infusion, and those small-volume Injections for which the monographs specify such requirements, are subject to the particulate matter limits set forth under *Particulate Matter in Injections* ⟨788⟩. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 mL or less if the individual monograph includes a test for *Particulate Matter;* it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter.*~~

▲All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* ⟨788⟩ and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed ''visible particulates'') in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection

process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container whose contents shows evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container–closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume injections for single-dose infusion and small-volume injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in *Particulate Matter in Injections* ⟨788⟩, unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume injection meets the requirements set forth for small-volume injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for *Particulate Matter in Injections* ⟨788⟩; it meets the requirements set forth for large-volume injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections administered exclusively by the intramuscular or subcutaneous route or packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter in Injections* ⟨788⟩.▲*USP29*

BRIEFING

⟨**11**⟩ **USP Reference Standards,** *USP 28* page 2204, page 3290 of the *First Supplement,* the *First Interim Revision Announcement* on page 33 of *PF* 31(1) [Jan.–Feb. 2005], the *Second Interim Revision Announcement* on page 357 of *PF* 31(2) [Mar.–Apr. 2005], the *Third Interim Revision Announcement* on page 710 of *PF* 31(3) [May–June 2005], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 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 710 of *PF* 29(3) [May–June 2003], page 1137 of *PF* 29(4) [July–Aug. 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 998 of *PF* 30(3) [May–June 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], and page 822 of *PF* 31(3) [May–June 2005].

(HDQ) RTS—33667-1; 38378-4; 39405-1; 40243-1; 40762-3; 41201-1; 41201-2; 41571-2; 41750-1; 41818-1; 41818-2; 41818-3; 41818-4; 41979-1; 41979-2; 41987-1; 42060-1; 42060-2; 42082-1; 42082-2; 42612-1; 42635-1

Add the following:

■**USP Beta Alanine RS [**3-aminopropionic acid**]**—[To come.]■2S (*USP29*)

Add the following:

■**USP Amino Methacrylate Copolymer RS**—Dry at 110° for 3 hours. Keep container tightly closed. Store at or below room temperature.■2S (*USP29*)

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Add the following:

■**USP L-Arabinitol RS** [L-arabitol, 1,2,3,4,5-pentanepentol] ($C_5H_{12}O_5$ ✧ 152.15)—[To come.]■2S (*USP29*)

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-benzazepine-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 (*USP29*)

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-benzazepine-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 (*USP29*)

Add the following:

■**USP Benazepril Related Compound C RS** [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] ($C_{22}H_{24}N_2O_5$ ✧ 396.44—Dry portion in vacuum at 105° for 4 hours before using.■2S (*USP29*)

Add the following:

■**USP Benazepril Related Compound D RS** [(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]—[To come.]■2S (*USP29*)

Add the following:

■**USP Benazepril Related Compound E RS** [3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid]—[To come.]■2S (*USP29*)

Add the following:

■**USP Benazepril Related Compound F RS** [*tert*-butyl-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid]—[To come.]■2S (*USP29*)

Add the following:

■**USP Benazepril Related Compound G RS** [(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]—[To come.]■2S (*USP29*)

Add the following:

■**USP Desmopressin Acetate RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Erythritol RS** [*meso*-erythritol, 1,2,3,4-butanetetrol] ($C_4H_{10}O_4$ ✧ 122.12)—[To come.]■2S (*USP29*)

Add the following:

■**USP Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion RS**—Dry at 105° for 1.5 hours before use.■2S (*USP29*)

Add the following:

■**USP Fluticasone Propionate Related Compound F RS** [6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid]—[To come.]■2S (*USP29*)

Add the following:

■**USP Galactitol RS** [dulcitol] ($C_6H_{14}O_6$ ✧ 182.17)—[To come.]■2S (*USP29*)

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Add the following:

■**USP Hyoscamine Related Compound A RS** [norhyoscyamine sulfate or (1*R*,3*R*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl(2*S*)-3-hydroxy-2-phenylpropanoate]—[To come.]■2S (*USP29*)

Add the following:

■**USP Nefazodone Hydrochloride RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Nefazodone Related Compound A RS** [1-(3-chloropropyl)-4-(chlorophenyl)piperazine] ($C_{13}H_{18}Cl_2N_2$ ✧ 273.20)—[To come.]■2S (*USP29*)

Add the following:

■**USP Nefazodone Related Compound B RS** [2-(3-(4-(chlorophenyl)-1-piperazinyl)propyl)-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3*H*-1,2,4-triazol-3-one] ($C_{25}H_{32}ClN_5O_2$ ✧ 470.01)—[To come.]■2S (*USP29*)

Add the following:

■**USP Pamidronate Disodium RS**—[To come.]■2S (*USP29*)

Delete the following:

~~■**USP Paroxetine Related Compound A RS** [*trans*-4-(*p*-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine hydrochloride]—Do not dry before use. Keep container tightly closed. Protect from light.~~■2S (*USP29*)

Add the following:

~~▲**USP Paroxetine Hydrochloride for System Suitability RS**~~ ■**USP Paroxetine System Suitability Mixture A RS**■2S (*USP29*)—Mixture of 1% paroxetine related compound A [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3 *S-trans*); and 1% of paroxetine related compound B [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl)-, hydrochloride (3 *S-trans*)] in a matrix of paroxetine hydrochloride.▲*USP29*

Add the following:

■**USP Phenylethyl Alcohol RS** ■($C_8H_{10}O$ ✧ 122.17)—[To come.]■2S (*USP29*) ■2S (*USP28*)

Add the following:

■**USP Sodium Salicylate RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Tazobactam RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Tazobactam Related Compound A RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Travoprost RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Travoprost Related Compound A RS** [(5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid] ($C_{23}H_{29}F_3O_6$ ✧ 458.52)—[To come.]■2S (*USP29*)

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Chemical Tests and Assays

OTHER TESTS AND ASSAYS

BRIEFING

⟨**401**⟩ **Fats and Fixed Oils,** *USP 28* page 2310. It is proposed to revise the test for *Acid Value (Free Fatty Acids)* to include the formula.

(EMC: C. Sheehan) RTS—42638-1

Change to read:

ACID VALUE (FREE FATTY ACIDS)

The acidity of fats and fixed oils in this Pharmacopeia may be expressed as the number of mL of 0.1 N alkali required to neutralize the free acids in 10.0 g of substance. Acidity is frequently expressed as the Acid Value, which is the number of mg of potassium hydroxide required to neutralize the free acids in 1.0 g of the substance.

Procedure—Unless otherwise directed, dissolve about 10.0 g of the substance, accurately weighed, in 50 mL of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with 0.1 N sodium hydroxide) contained in a flask. If the test specimen does not dissolve in the cold solvent, connect the flask with a suitable condenser and warm slowly, with frequent shaking, until the specimen dissolves. Add 1 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS until the solution remains faintly pink after shaking for 30 seconds. Calculate either the Acid Value or the volume of 0.1 N alkali required to neutralize 10.0 g of specimen (free fatty acids), whichever is appropriate.

■Calculate the Acid Value by the formula:

$$56.1V \times N/W$$

in which V is the volume, in mL, and N is the normality, respectively, of the sodium hydroxide solution; and W is the weight, in g, of the sample taken.■2S (*USP29*)

If the volume of 0.1 N sodium hydroxide VS required for the titration is less than 2 mL, a more dilute titrant may be used, or the sample size may be adjusted accordingly. The results may be expressed in terms of the volume of titrant used or in terms of the equivalent volume of 0.1 N sodium hydroxide.

If the oil has been saturated with carbon dioxide for the purpose of preservation, gently reflux the alcohol-ether solution for 10 minutes before titration. The oil may be freed from carbon dioxide also by exposing it in a shallow dish in a vacuum desiccator for 24 hours before weighing the test specimens.

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1058**⟩ **Analytical Instrument Qualification,** page 233 of *PF* 31(1) [Jan.–Feb. 2005]. This new general information chapter, which previously appeared in *Pharmacopeial Previews,* is now forwarded with minor editorial changes to *In-Process Revision.* The Expert Committee recognizes that the current chapter does not address corrective and preventive actions when a periodic PQ fails. Readers are encouraged to submit comments to USP regarding these or any other relevant issues.

(PA4: H. Pappa) RTS—41837-1

Add the following:

■⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of instruments and tools, ranging from simple nitrogen evaporators to complex multiple-function technologies, are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use and that they do not pose high safety risks. The analyst's objective is to consistently obtain reliable and val-

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id data suitable for the intended purpose. Depending on the applications, users validate their procedures and perform system suitability tests and in-process quality control checks to help ensure that the acquired data are reliable. These activities help enhance the quality of data, and there are specific guidances and procedures for performing the activities. With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions abound regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification, approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data.

Validation versus Qualification

Because there is ambiguity in the use of the terms ''validation'' and ''qualification'', in this chapter the term ''validation'' will be used for processes and software, and the term ''qualification'' will be used for instruments. Thus, the phrase ''analytical instrument qualification'' (AIQ) is used for the process of ensuring that an instrument is suitable for its intended application. The term ''validation'' is reserved for processes including analytical procedures and software procedures.

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the base for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control checks. These quality components are described below.

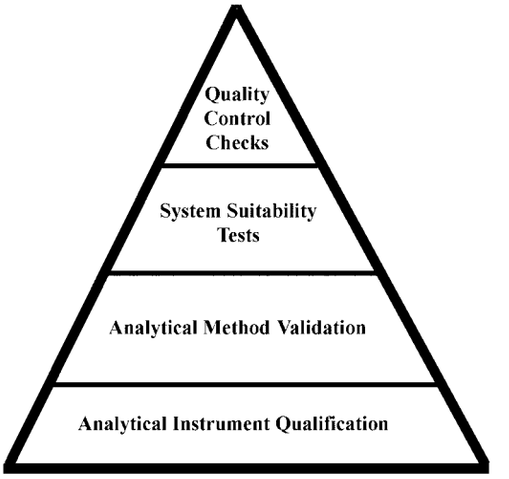

Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure does what it purports to do and addresses the required attributes of the procedure. Use of a validated procedure provides confidence that the procedure will generate test data of acceptable quality. Users of compendial procedures perform validation using the criteria provided in general information chapter *Validation of Compendial Methods* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform according to the analyst's expectations and according to the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. USP general chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests.

Quality Control Checks

Most analyses are performed on instruments calibrated or standardized using reference materials or calibration standards. The calibration or standardization process uses a single- or multiple-point calibration, depending on the instrument and the intended application. The calibration or standardization of an instrument during analysis ensures that the instrument response correlates with the known quantity or quality of the calibration standard or reference material. In addition to calibration or standardization, some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance.

The extent of system suitability tests or quality control checks varies for different analyses, depending on their intended use. Chemical analyses, which are largely subject to Good Manufacturing Practices (GMP) regulations and require tighter precision and accuracy, may require more system suitability tests than bioanalytical work, which is largely subject to Good Laboratory Practice (GLP) regulations. Bioanalytical work requires sensitive, specific, broad-range analysis and therefore is generally performed with more quality control checks during sample analysis. Control check samples are also appropriate when high-variability tests or instruments (i.e., those with a relative standard deviation [RSD] higher than 5%) are considered. Other use-specific considerations may also determine the extent of system suitability tests or quality-control-check sample analysis. Whatever the case, the sum total of such controls provides an important step in delivering quality data for the intended purpose.

In summary, analytical instrument qualification and analytical method validation ensure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks ensure the quality of analytical results *immediately before* or *during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical data—analytical method validation, system suitability tests, and quality control checks—are not within the scope of this chapter.

Qualification Phases

Instrument qualification is not a single continuous process, but instead results from several discrete activities. For convenience, these activities can be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Some of these qualification terms have their roots in manufacturing-process validation. Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Also, some AIQ activities cover more than one qualification phase and could arguably be performed within any of the phases. It is important that the required AIQ activities be performed; however, within which qualification phase an activity is performed or reported is not as important. *Table 1* accommodates these overlapping activities by letting users perform them under one or another phase as necessary. The user should describe where the activity is performed and reported.

Table 1. Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification*

DQ	IQ		OQ		PQ
Timing and applicability					
Prior to purchase of a new type of instrument	At installation of each instrument (new, old, or existing unqualified)		After installation or major repair of each instrument		Periodically at specified intervals for each instrument
Activities					
Assurance of vendor's DQ	System description	⇆	Fixed parameters		Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery				SOPs for operation, calibration, and maintenance
Instrument's fitness for use in laboratory	Utilities/facility/ environment				
	Network and data storage	⇆	Secure data storage, backup, and archive		
	Assembly and installation				
	Installation verification	⇆	Instrument function tests	⇆	Performance checks

* Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Such activities spanning more than one qualification phase are shown as connected by double arrows. If an activity listed under a given phase is performed under another phase, it is not necessary to repeat the activity under the phase where the activity is listed. Performing the activity is far more important than the phase under which the activity is performed.

DESIGN QUALIFICATION

Design qualification (DQ) is most suitably performed by the instrument developer or manufacturer. Because the instrument design is already in place for commercial off-the-shelf (COTS) systems, users do not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature of the instrument, the complexity of the proposed application, and the extent of the user's previous interaction with the manufacturer. Vendor audits or required vendor-supplied documentation satisfy part of the DQ requirements. The required scope and comprehensiveness of the audits and documentation vary with users' familiarity with the instrument and their previous interactions with the vendor.

Informal processes also form an important part of DQ. Informal personal communications and networking with peers at technical or user-group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Informal site visits to other users' and vendors' facilities to obtain data on representative samples that used the specified instrument are another good source of information about suitability for intended use. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection.

INSTALLATION QUALIFICATION

Installation qualification (IQ) is the documented collection of activities necessary for installing an instrument in the user's environment. IQ applies to an instrument that is new or was pre-owned, or to any instrument that exists on site but has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been packed and transported to another location. The activities and documentation associated with IQ are as follows.

System Description—Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flow charts where appropriate.

Instrument Delivery—Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment—Verify that the installation site satisfactorily meets vendor-specified environmental requirements. A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.

Network and Data Storage—Some analytical systems require users to provide network connections and data storage capabilities at the installation site. When required, connect the instrument to the network, and check its functionality.

Assembly and Installation—Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and install simple ones. For complex

instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. If the preowned, unqualified existing instrument or transported instrument requires assembly and installation, perform the tasks as specified above, then perform the installation verification procedure, described below.

Installation Verification—Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and, when present, the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

OPERATIONAL QUALIFICATION

After a successful IQ, the instrument is ready for OQ testing. The OQ phase may consist of these test parameters.

Fixed Parameters—These tests measure the instrument's nonchanging parameters such as length, height, weight, voltage inputs, acceptable pressures, and loads. If the vendor-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need redetermination. [NOTE—These tests could also be performed during the IQ phase (see *Table 1*); if so, fixed parameters need not be redetermined as part of OQ testing.]

Secure Data Storage, Backup, and Archiving—When required, test secure data handling such as storage, backup, and archiving at the user's site according to written procedures.

Instrument Function Tests—Important instrument functions should be tested to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter. Nevertheless, as a guide to the types of tests possible during OQ, consider the following, which apply to an HPLC unit:

- pump flow rate
- gradient linearity
- detector wavelength accuracy
- detector linearity
- column oven temperature
- injector precision and accuracy
- peak retention time precision

Routine analytical tests do not constitute OQ testing. OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment, and repeating the testing at regular intervals may not be required. However, when the instrument undergoes major repairs or modifications, relevant OQ tests should be repeated to verify whether the instrument continues to operate satisfactorily. Relevant OQ tests should also be repeated for an instrument that has been transported to another location, although a move within the laboratory, or from one room to another, that does not disturb instrument operation may not require requalification.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification and

should be performed whenever possible. Holistic tests, which involve the entire system, are acceptable in lieu of modular testing. Having successfully completed OQ testing, the instrument is qualified for use in regulated samples analysis.

PERFORMANCE QUALIFICATION

After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through performance qualification (PQ). The PQ phase includes the following parameters.

Performance Checks—Set up a test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. PQ tests should be performed routinely on a working instrument, not only on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble-free instrument operation for the intended applications. PQ tests should be performed independently of the routine analytical testing performed on the instrument. As is the case with OQ testing, PQ tests can be modular or holistic. However, because many modules within a system interact, holistic tests generally prove to be more effective because they evaluate the entire system, not simply the system's individual modules.

Testing frequency depends on the ruggedness of the instrument and the criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. It may also be scheduled for regular intervals, such as weekly or monthly. Experience with the instrument can influence this decision. Generally, the same PQ tests are repeated each time so that a history of the instrument's performance can be compiled. Some system suitability tests or quality control checks that are performed concurrently with the test samples also imply that the instrument is performing suitably. However, although system suitability tests can supplement periodic PQ tests, they cannot replace them.

Preventive Maintenance and Repairs—When an instrument fails to meet PQ test specifications, it requires maintenance or repair. A periodic preventive maintenance may also be recommended for many instruments. The relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Standard Operating Procedure[s] for Operation, Calibration, and Maintenance—Establish standard operating procedures to maintain and calibrate the instrument. Use a logbook, binder, or electronic record to document each maintenance and calibration activity.

Roles and Responsibilities

USERS

Users are ultimately responsible for instrument operations and data quality. The user's group encompasses analysts, their supervisors, and organization management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments, because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, validation specialists, and quality assurance (QA) personnel can advise and assist as needed,

but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

QUALITY ASSURANCE

The QA role in AIQ remains the same as for any other regulated study. QA personnel should understand the instrument qualification process, and they should learn about the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it meets regulatory requirements, and they should make certain that the users attest to the scientific validity of the process.

MANUFACTURERS

Manufacturers and developers are responsible for DQ when designing the instrument. They are also responsible for validation of relevant processes used in manufacturing and assembly of the hardware and for software associated with the instrument. Manufacturers and developers are also responsible for writing stand-alone software for analytical work in a documented quality manner and for the validation of this software. Manufacturers should test the assembled instruments before shipping them to users.

Manufacturers and vendors should make available to users a summary of their validation efforts and the results of final instrument and software tests, and they should provide the critical functional test scripts that can be used to qualify the instrument and software at the user site. For instance, manufacturers and vendors can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, manufacturers and vendors should notify all known users about hardware or software defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

SOFTWARE VALIDATION

Software used for analytical work can be classified into three categories: firmware; instrument control, data acquisition, and processing software; and stand-alone software.

Firmware—Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users generally cannot alter firmware design or function. Firmware is thus considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware. So when the hardware (that is, the analytical instrument) is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see *Change Control,* below).

Instrument Control, Data Acquisition, and Processing Software—Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and postacquisition calculations. Thus both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire

instrument and software system, is more efficient than modular validation of the software alone. Thus the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process.

Stand-Alone Software—An authoritative guide for validating stand-alone software, such as LIMS, is available.[1] The validation process is administered by the software developer, who also specifies the development model appropriate for the software. Validation takes place in a series of activities planned and executed through various stages of the development cycle.

The software validation guide cited in the previous paragraphs indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only part of the validation process for stand-alone software and does not constitute complete validation. Refer to the software validation guide for activities that must be performed at the user site for testing stand-alone software used in analytical work.

Change Control

Changes to the instrument and software become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required. The change control process enables them to do this.

Change control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below:

Operational Qualification—Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.

Performance Qualification—Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In the future, perform the revised PQ testing.

For changes to firmware and to software for instrument control, data acquisition, and processing, change control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change control for stand-alone software requires user-site testing of changed functionality.

AIQ Documentation

Two types of documents result from AIQ: static and dynamic.

STATIC DOCUMENTS

Static documents are obtained during the DQ, IQ, and OQ phases and should be kept in a ''Qualification'' binder. Where multiple instruments of one kind exist, documents common to all instruments should go into one binder or section, and documents specific to an instrument should go into

[1] *General Principles of Software Validation: Final Guidance for Industry and FDA Staff,* U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, January 11, 2002. http://www.fda.gov/cdrh/comp/guidance/938.html (accessed September 2004).

that instrument's binder or section. During change control, additional documents can be placed with the static ones, but previous documents should not be removed. When necessary, such documents may be archived.

DYNAMIC DOCUMENTS

Dynamic documents are generated during the OQ and PQ phases when the instrument is maintained or tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them. These documents may also be archived as necessary.

Instrument Categories

Modern laboratories typically include a suite of tools varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of principles to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Examples of instruments in each group are provided. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site. That category should be determined by users for their specific instruments or applications.

GROUP A

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Examples of instruments in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, and glass pipets.

GROUP B

Conformance of Group B instruments to user requirements is determined according to an instrument's standard operating procedures. Conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple, and causes of their failure are readily discernible by simple observation. Examples of instruments in this group are balances, incubators, IR spectrometers, melting point apparatus, muffle furnaces, light microscopes, pH meters, variable pipets, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, and viscosimeters.

GROUP C

Conformance of Group C instruments to user requirements is complex and highly method-specific; conformity bounds are determined by the application. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Examples of instruments in this group include the following:

- atomic absorption spectrometers
- differential scanning calorimeters
- electron microscopes
- flame absorption spectrometers
- high-pressure liquid chromatographs
- mass spectrometers
- microplate readers
- thermal gravimetric analyzers
- X-ray fluorescence spectrometers
- densitometers
- diode-array detectors
- elemental analyzers

- gas chromatographs
- near IR spectrometers
- Raman spectrometers
- UV/Vis spectrometers
- inductively coupled argon–plasma emission spectrometers

Again, it must be emphasized that the placement of these instruments in the given three groups is for illustrative purposes only. The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

CONCLUSION

The purpose of the use of analytical instruments is to generate reliable data. Analytical instrument qualification helps fulfill this purpose. No authoritative guide existed that considered the risk of instrument nonperformance and combined that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments became a subjective and often fruitless document-generating exercise.

This chapter is based on the outcome of a user workshop-conference on the subject and provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The process provided in this chapter focuses on scientific value rather than on producing documents. Implementing such a process should increase efficiency and remove ambiguous or varying interpretations by different groups.■2S (*USP29*)

BRIEFING

⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis. This new general information chapter, which previously appeared in *Pharmacopeial Previews* on page 1650 of *PF* 28(5) [Sept.–Oct. 2002], is now forwarded to *In-Process Revision.* The chapter is based on the *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients*, prepared by The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). The chapter defines the required elements of a Certificate of Analysis, provides a template for organizing required and optional data in a logical manner, and assists in establishing a uniform understanding of the roles and responsibilities of excipient manufacturers, distributors, and users.

This proposed chapter, published with the permission of IPEC-Americas, is informational and contains no standards, tests, assays, or other mandatory specifications with respect to any Pharmacopeial article.

On the basis of comments received, allowances are made to include materials that do not meet certain compendial requirements as compendial materials, with labeling requirements to state the deficiencies; and clarification is made to the *Compendial Designation* section by the deletion of a reference to *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩, because these are not the only recognized principles of good manufacturing practices. Because this chapter is presented as a general information chapter, editorial changes have been made to exclude terms such as "required" and "must"; also other minor editorial changes have been made.

(ETM: J. Lane) RTS—39715-1

Add the following:

■⟨1080⟩ BULK PHARMACEUTICAL EXCIPIENTS—CERTIFICATE OF ANALYSIS

BACKGROUND

This general information chapter is derived from the *Certificate of Analysis Guide for Bulk Pharmaceutical Excipients,* prepared by The International Pharmaceutical Excipients Council of the Americas (IPEC-Americas), an international guidance document on the preparation and appropriate use of a Certificate of Analysis (COA) for these excipients, referenced throughout the chapter as "excipient(s)". The chapter defines the ~~required~~ suggested elements of a Certificate of Analysis, provides a template for organizing required and optional data in a logical manner, and as-

In-Process Revision

sists in establishing a uniform understanding of the roles and responsibilities of excipient manufacturers, distributors, and users.

The principles and information in this chapter can be applied to the manufacture of all bulk pharmaceutical excipients intended for use in human drugs, veterinary drugs, and biologics. As an international guidance document, it cannot specify all national legal requirements nor cover in detail the particular characteristics of every excipient. When considering how to use this chapter, each manufacturer, distributor, or user ~~must~~ should consider how it may apply to that specific manufacturer's product and processes. The diversity of excipients means that some principles of the chapter may not be applicable to certain products and processes.

The chapter is divided into several parts. The first part provides background discussion necessary for the design and ~~required~~ suggested elements of a COA. A template is provided to show the format and placement of information in the COA. This is followed by a detailed discussion to ensure that the purpose and meaning of the specific information contained in the COA is understood. For a list of terms used in this information chapter and their definitions, see *Appendix 1*.

GENERAL GUIDANCE

International regulations governing drugs require that components of the drugs be manufactured, processed, packed, and held in accordance with good manufacturing practices (GMPs). For a thorough discussion of GMPs that apply to excipient manufacture, see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩. The excipient is often a natural substance, mixture, or polymer whose chemical and physical properties are difficult to quantify and that is often used with a broad range of active pharmaceutical ingredients and in a diverse range of finished dosage forms. Until now, there were no guidance documents that specifically focused on the content or format of COAs for excipients and that addressed the diversity of both the excipients and their usage.

Preparation and Appropriate Use of a Certificate of Analysis—The Certificate of Analysis for excipients should be prepared and issued by the supplier of the material, following the general guidelines discussed below. Primary responsibility for the preparation of the COA belongs to the excipient manufacturer. It is most important that a complete and accurate COA be provided to the excipient user for specific lots or batches intended for use in the pharmaceutical industry. Additional considerations ~~must~~ should be made for the preparation and issuance of a COA by a distributor of excipients.

The user of a bulk pharmaceutical excipient should always receive a COA for material to be used in the manufacture of a drug product. At a minimum, the user should perform adequate identification tests on each lot of excipient received before releasing it for use in the drug product. Specific identity tests should be used whenever possible. It is a regulatory requirement that excipients be assessed for conformity with all appropriate specifications. However, testing of all specification parameters may not be required for lot release if adequate compliance assurances are provided on the supplier's COA. Before using an excipient in a pharmaceutical product based on COA data, the user also ~~must~~ should have an understanding of the supplier's control systems and compliance with GMPs, through appropriate auditing or qualification of the supplier.

Nevertheless, it is the responsibility of the user of the excipient to verify any of the analytical data contained in the COA if knowledge of such information is deemed essential

to the use of that excipient. Such testing may go beyond the scope of the compendial methods described in the *NF*, or beyond those used to develop the information in the COA.

To use test results from a COA, the user must also establish the reliability of the supplier's COA test results by periodically performing all required tests and comparing the results obtained to the supplier's test results. Occasionally, it may not be possible to perform all the required tests because of special equipment requirements, etc., that may not be available to the user. Performing fewer than all these tests may be acceptable provided that the reliability of the supplier has been adequately determined using other appropriate supplier qualification techniques.

It is important to understand that these results may not always specifically correlate, especially when an excipient is produced as a continuous lot. However, the user's test results should demonstrate compliance with the specification requirement.

Use of Contract Facilities—Contract facilities are frequently used in the manufacture, testing, and distribution of excipients. When such facilities are used, the supplier of the excipient has the obligation to ensure that the facilities operate under appropriate quality standards (i.e., cGMP, GLP, etc.).

DESIGN AND ~~REQUIRED~~ SUGGESTED ELEMENTS OF A CERTIFICATE OF ANALYSIS

The ~~required~~ suggested elements of a COA are listed below and are included in the following *Certificate of Analysis Template* section of this chapter. Excipient suppliers may organize the ~~required~~ suggested elements presented in the COA template at their discretion; however, the parts of the template were designed to present the ~~required~~ suggested and optional information in a logical manner. For a detailed description of each element and examples of statements, see the appropriate section below in this chapter.

The origin and the identity of the excipient are typically established in a *Header* section. The manufacturer and manufacturing site ~~must~~ should be identified if different from the supplier and supplier location, enabling the user to make certain that the excipient comes from a qualified source. Although the manufacturer ~~must~~ should be made known to the user, the use of codes for manufacturers and manufacturing sites on the COA to protect confidentiality is acceptable. The identity of the excipient must be definitively established by stating the compendial and trade name, the grade of the material, and applicable compendial designations.

A lot/batch number or other means of uniquely identifying the quantity of material covered by the COA and information relating specifically to it are typically included in a *Body* section. The lot number or other unique identification of the material, its date of manufacture, and product code or number ~~must~~ should be stated and traceable to a specified lot. If applicable, the expiration date, recommended re-evaluation date, or other relevant statement regarding the stability of the excipient is typically included in this section. Any information required by the customer would also be included here.

The actual test results applicable to the quantity of material covered by the COA are included in an *Analysis* section. The test name, the result, the acceptance criteria or specifications, and a reference to the test method used ~~must~~ should be included for each characteristic listed. Reporting of actual data and observations is recommended rather than nonspecific ''passes'' or ''conforms'' statements. If the reported results are derived from a skip-lot or reduced frequency testing program, or an average or in-process test result, this ~~must~~ should be noted on the COA.

The *Certification and Compliance Statement* section is used to list various types of statements that may be required depending on the excipient and specific user needs. These statements are usually negotiated between supplier and user based on specific application requirements. Any declaration of the supplier that includes compliance of additional compendial or other regulatory requirements is typically included in this section.

Many excipients have applications other than pharmaceuticals, such as food, cosmetics, or industrial products. Any product listed as being in compliance with specific regulations ~~must~~ should meet the specifications and requirements of that regulation and must be manufactured under appropriate GMPs.

The identity of the individual approving the content of the COA ~~must~~ should appear on the COA. The page number and total number of pages ~~must~~ should also appear on the COA. This information is usually included in a *Footer* section.

CERTIFICATE OF ANALYSIS TEMPLATE

Listed below is a template for the content and format of a COA.

Header

- Titled "Certificate of Analysis"
- Company Name, Address, Phone Number, and Identity of Manufacturer and Manufacturing Site
- Name (compendial/trade) of Excipient
- Grade of Excipient
- Compendial Designation

Body

- Lot/Batch Number
- Date of Manufacture
- Product Code or Number
- Expiration Date (if required)
- Recommended Re-Evaluation Date (if required)
- Stability Statement (if required)
- Customer Required Information

Analysis

- Test Name
- Test Results
- Acceptance Criteria (i.e., specifications)
- Reference to the Test Method
- Reference to Skip-Lot Testing (if appropriate)
- Reference to Average or In-Process Test Results (if appropriate)
- Date Retested (if appropriate)
- Summary of Noncompendial Testing (if any)

Certification and Compliance Statements

- GMP Compliance ~~(IPEC excipient GMPs)~~
- Additional Regulatory References
- Potential to Meet Additional Compendial Standards
- Content Listing and Grade of Ingredients (if a mixture)
- Other Specific Compliance Statements [e.g., organic volatile impurities (OVI), residual solvents, transmissible spongiform encephalopathy (TSE), etc.]

Footer

- Identity of Authorized Individual for Approval
- Date of Approval
- Page Number (i.e., 1 of __)

COMPENDIAL DESIGNATION

For a supplier to claim a compendial grade on the COA for an excipient, two requirements ~~must~~ should be met. The first requirement is that the excipient be manufactured according to recognized principles of GMPs (see ~~*General Notices* and *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩~~ *General Notices and Requirements*). Adequate conformance to GMPs ~~must~~ should also be demonstrated for subsequent steps in the distribution of the excipient. The second requirement is that the excipient meet all the specifications contained in the appropriate compendial monograph, unless its difference is stated on its label, as defined under *General Notices and Requirements.* When an excipient is listed as compendial grade, it is understood that the above requirements have been met for the material, and the user would be able to confirm this through an appropriate audit of the supplier.

Compendial standards define what is considered an acceptable article and also 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 supplier's release specifications and compliance with GMPs are developed and followed to ensure that the article, when stored correctly, will comply with compendial standards until its expiration or recommended re-evaluation date.

Every compendial article shall be so constituted that when examined in accordance with these assay and test procedures, it meets all the requirements in the monograph defining it, as well as meeting any provisions under *General Notices and Requirements* and in the general chapters, as applicable. 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 ensuring compliance with compendial 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 examination of finished units drawn from the batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the supplier when judging compliance of the batch with the compendial standards.

DATES ON A CERTIFICATE OF ANALYSIS

Part of the overall goal to standardize COA for excipients includes a provision for the consistent reporting of appropriate, meaningful, and well-defined dates. The discussion below indicates specific dates that are expected on the COA, along with definitions of the dates, in order to provide suppliers and users of excipients with a mutual understanding of their meaning. Use of the recommended terminology will be helpful in reducing the number of questions on dating information reported for excipients. Use of terminology other than that discussed below is discouraged, because the terms may be ill-defined and have different meanings for the excipient supplier and user. Examples of such terms that should **not** be used include ''shelf life'', ''use-by date'', ''warranty date'', and ''expiration period''.

In reporting dates on COA for excipients, it is important that a clear and unambiguous format be used to prevent possible misinterpretation. To accomplish this, it is recommended that an alpha designation be used for the month (may be abbreviated), rather than a numerical representation. It is also recommended that the year include all 4 digits (e.g., Jan. 1, 2005, or 1 Jan. 2005).

Date of Manufacture—The date of manufacture ~~must~~ should be included on the COA for each excipient lot and should be assigned by the suppliers on the basis of their established policies and procedures. It is recognized that excipients may be manufactured using a variety of processes (e.g., continuous or batch) that may require a period of several days or more to complete. In addition, some excipients may be mixtures or blends of other excipients, and excipient production may include reprocessing steps. Because of this diversity, the date of manufacture should be clearly defined by the supplier and consistently applied for the particular excipient and process. In reporting the date of manufacture, the excipient supplier should indicate the date of completion of the final manufacturing process (as defined by the supplier).

It is important to note that repackaging alone is not considered a processing step to be used in determining the date of manufacture. To provide traceability for a specific excipient lot, other dates may be required in addition to the date of manufacture in order to to reflect additional steps such as repackaging.

Expiration Date and Recommended Re-Evaluation Date—The stability of excipients may be an important factor in the stability of the finished pharmaceutical dosage forms that contain them. Many excipients are very stable and may not require extensive testing to demonstrate continued conformance to appropriate specifications. Other excipients may undergo chemical, physical, and microbiological changes over time that cause the material to fall outside established specifications.

Appropriate expiration and/or recommended re-evaluation dates for excipients should be established from the results of a documented stability-testing program or from historical data. The testing program should include defined and controlled storage conditions (e.g., temperature and humidity), a consideration of different packaging types that may be used as market containers, and meaningful, specific test methods to adequately assess the stability characteristics of the excipient. Stability testing should determine whether possible degradation, moisture gain or loss, viscosity changes, or other possible changes occur to make the excipient unacceptable for use (e.g., unstable or hygroscopic materials). For additional information on excipient stability, see *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* ⟨1078⟩.

The expiration date for an excipient is defined as the date after which the supplier recommends that the material should not be used. Prior to the assigned expiration date, the excipient is expected to remain within established specifications, if stored according to the supplier's recommended conditions.

The recommended re-evaluation date for an excipient is the date suggested by the supplier after which the material should be re-evaluated to ensure continued compliance with specifications. Re-evaluation of the excipient may include physical inspection and appropriate chemical, physical, and microbiological testing. Prior to the re-evaluation date, the excipient is expected to remain within established specifications, provided it has been stored according to the supplier's recommended conditions. But beyond the recommended re-evaluation date, the excipient should not be used without adequate evaluation at appropriate intervals, to determine whether the material continues to be acceptable for use. The recommended re-evaluation date differs from the expiration date in that the excipient may be re-evaluated to extend the length of time the material may be used, if supported by the results of the evaluation and appropriate stability data.

In reporting the expiration and recommended re-evaluation dates, the excipient supplier is providing important information to the user about the stability of the material. As discussed previously, the assignment of an expiration date and a recommended re-evaluation date should be based on appropriate evaluation of potential changes that may occur in the material's properties. It is acceptable to report both an expiration date and a recommended re-evaluation date on the COA for excipients, if applicable, but both dates may not always be required. Expiration and recommended re-evaluation dates should not be reported by a supplier without sufficient stability data or product history to support the assigned dates.

For excipients determined to be very stable (greater than 2 years), either the specific expiration date and/or the recommended re-evaluation date should be reported on the COA for the material, or a general stability statement may be included (e.g., stability greater than 2 years). If available data indicate that an excipient has limited stability (2 years or less) under anticipated storage conditions, a specific expiration date and/or recommended re-evaluation date ~~must~~ should be reported on the COA for the material.

If long-term stability data are not available for an excipient, an appropriate statement should be included on the COA to indicate what is known about the stability of the material and whether stability studies are in progress.

Date Retested—If retesting is performed by an excipient supplier and the results are used to extend the length of time that the material may be used, the date retested should also be reported on the COA. The specific tests that were subject to retesting should be clearly identified, and the results obtained upon retesting should be reported. After retesting, a new recommended re-evaluation date should be reported on the COA.

Additional Dates—Other dates may appear on a COA, if desired by the excipient supplier or requested by the user. Examples include the release date, shipping date, date of testing, and date the COA was printed or approved. Any additional dates that appear on a COA for excipients ~~must~~ should include a clear indication of what the date represents or means.

TESTING FREQUENCY

For the excipients listed in the *USP–NF*, the product specifications are set by the supplier to include all parameters listed in the monograph. It is not required that analysis of all specification parameters be made on each lot (see *General Notices and Requirements*). However, sufficient analysis and process validation data ~~must~~ should exist to ensure that the lot meets all specifications before it is released. This is an established practice that has been successfully used in industry for many years. Periodic testing of all parameters should be performed to revalidate the control system. The frequency of these periodic tests should be determined by the suppliers on the basis of their understanding of the manufacturing control system. At a minimum, the parameters should be checked once a year.

For excipients that are not included in *USP–NF*, specifications should be set by the supplier to ensure that the quality of the material is maintained on a continuing basis and reflects both the excipient manufacturing process and inherent properties. The analytical methods used to evaluate the characteristics of noncompendial excipients may be the same as those contained in the compendia, or may be unique to the supplier or the material. The methods should be demonstrated to provide accurate, reproducible, and consistent results for the characteristic being tested. It may be appropriate for noncompendial excipients to have some tests performed at reduced frequency.

The excipient user should evaluate the supplier's specifications and methods to ensure that they are appropriate and acceptable for the quality control needed for the manufacturing process of their drug product. The user ~~must~~ should determine which of the supplier's specifications and methods are required for release of the excipient for use in their process. If additional tests or alternative methods are required by the user, appropriate specifications and methods, along with responsibility for performing the testing, must be agreed upon by the excipient supplier and user.

Reduced Frequency Testing—When analysis of some parameters is carried out at a reduced frequency (for example, every 10th lot), this ~~must~~ should be clearly stated on the COA. Each specific test subject to reduced frequency testing ~~must~~ should be indicated. Reduced frequency testing should be used only for excipients manufactured using a stable process. There ~~must~~ should be a sound technical basis and sufficient documentation to support testing any parameter at a reduced frequency. This would normally include the following points:

- Appropriate validation of the manufacturing process
- Process control—attribute charting (when appropriate)
- GMP controls

As part of the justification for reduced testing, it is important that there be assurances in place showing that the manufacturer's process complies with appropriate excipient GMP requirements.

Some tests, because of their significance, should always be performed on each lot, whereas others may be candidates for reduced frequency testing. Attribute testing results in qualitative data that provide pass/fail results or results expressed as less than or greater than a specified value. The result merely establishes compliance with a specification parameter. There are no data to indicate how well the material complies, as would be obtained from variable or quantitative test results.

Reduced frequency testing of an attribute requires that the manufacturer show that the qualitative parameter is in a state of statistical control. This necessitates tabulating the test results for consecutive lots produced.

Skip-Lot Testing—Skip-lot testing may be applied to an excipient that is made by either a batch or a continuous process. Various commonly accepted statistical sampling plans may be used to demonstrate appropriate process control. Examples of each are listed below:

EXAMPLE 1: For an average outgoing quality level (AOQL) of 1% and a test frequency of 1 in 10, the supplier ~~must~~ should find 100 consecutive lots in conformance. At a 2% AOQL and a test frequency of 1 in 10, the supplier would test 50 consecutive lots. For a 1% AOQL and a 1 in 5 test frequency, the supplier would test 70 consecutive lots. Nomographs are available to determine the test requirements.

EXAMPLE 2: When the excipient is manufactured by a continuous process, no discrete lot is produced. The sampling plan again is based upon the risk of approving a lot that was nonconforming. By testing 140 consecutive lots before going to a test frequency of 1 in 10, the plan establishes a low risk of approving a lot that is noncompliant.

Once the requirement is met, the supplier can monitor conformance to the specification parameter by testing 1 in 10 lots. Should any lot fail the analysis, the supplier ~~must~~ should return to 100% testing until the results once again meet the specification above.

Because excipients vary greatly in chemical and physical properties, the supplier of the excipient should determine which tests should be routinely performed and which tests may be appropriate for reduced frequency testing. This de-

termination must be justified and documented on the basis of the adequacy of the supplier's control system. Documentation ~~must~~ should be kept detailing the assumptions and the data supporting the skip-lot testing plan.

Type A and Type B Tests—Only certain types of tests are appropriate for reduced frequency testing. *Type A* is defined as tests that may not be easily controlled through standard process control techniques or that may change with time. These tests should normally be performed on each lot. *Type B* is defined as tests that normally can be controlled using standard process control techniques and that are not expected to change with time. These tests are candidates for reduced frequency testing. Examples of both types of tests are listed below:

Type A: Examples of Tests That Typically Need To Be Performed on Every Lot

- *Identification*—Required by GMPs for users (candidate for reduced frequency testing by suppliers)
- *Assay*—Critical quality parameter (if specified)
- *Viscosity*—Usually indicates grade
- *Loss on drying* (or moisture determination)—Indication of stability and appropriate process controls
- *Color*—Indication of stability and appropriate process controls
- *pH*—Indication of stability and appropriate process controls

Type B: Examples of Tests That May Be Candidates for Reduced Frequency Testing

- *Manufacturing impurities*—Based on starting materials and processes (e.g., Chloride, Sulfate, Nitrate, Glyoxal)
- *Heavy metals*
- *Lead*
- *Arsenic*
- *Residue on ignition*
- *Residual solvents*

This is not meant to be an exhaustive list of tests. It simply provides some direction on how a supplier can assess the importance of each test to the overall control of the process. Tests listed as possible candidates for reduced frequency testing (*Type B*) may need to be routinely tested (*Type A*), depending on the raw materials and process. Determinations can also be made for some *Type A* tests to become *Type B* tests. In a dedicated facility, identification testing by the supplier may not be necessary.

Documentation—The supplier of an excipient should develop and maintain documentation that outlines the process control systems and validation data to justify the use of reduced frequency testing. This documentation should also include procedures for handling the impact of significant changes on the reduced frequency testing program. For further information on excipient changes, see *Significant Change Guide for Bulk Pharmaceutical Excipients* ⟨1195⟩.*

The minimum number of lots to be fully tested for all specification parameters after a change has been made depends on the process and the significance of the change and should be based on sound statistical considerations.

Additionally, the documentation should contain procedures for re-evaluating the reduced frequency testing program when a testing failure occurs. Decisions regarding the continuance of reduced frequency testing ~~must~~ should be justified on the basis of the reasons for the failure and the supplier's ability to provide assurances that the reduced frequency testing program or other in-process parameters would identify these types of failures in the future.

* A draft of this new informational chapter appears elsewhere in this issue of *PF*.

Justifications for Reduced Frequency Testing—The following are examples of situations where a sound technical basis can be demonstrated and where reduced frequency testing might therefore be justified. [NOTE—There may be other such examples.]

- An impurity, by-product, or unreacted raw material could not be present in the product because the raw materials and chemical reactions used could not contain or generate such substances above the specified limits.
- The process capability index (*Cp*) on the relevant parameter is high and based on a stable process. Statistical analysis of the reduced frequency data should show that the property remains stable and within specifications. A process is considered stable when the output of the process, regardless of the nature of the processing (batch or continuous), can be demonstrated by appropriate means to show a level of variability that consistently meets all aspects of the stated specification (both Pharmacopeia-specific and customer-specific) and is thus acceptable for its intended use. For continuous processing, it is also important to demonstrate that the material has been produced under conditions in which the process has achieved a form of "steady state", i.e., in which there is minimal operator intervention and in which the in-process parameters have been stabilized (see *Appendix 2* for further definition of this concept and for determining levels of control).
- For a continuous process, the in-process analyses show that the property that is determined at reduced frequency is stable and within specification. Repeating the test on each lot would be redundant.
- An analysis that is determined on every lot has been shown to strongly correlate with an analysis that is run at a reduced frequency. The correlation shows that if a lot is within specification on the first analysis, it will be within specification on the second analysis.

USE OF ELECTRONIC SIGNATURES

Because of the growing dependence on computers and the need to accommodate paperless record systems, an electronic alternative to handwritten records and signatures is ~~required~~ suggested. Excipient suppliers have added computer information systems to enhance productivity.

The primary issue with transfer of a COA without a handwritten signature is the validation of data. There are several considerations that ~~must~~ should be met before an electronic signature or name attachment to a COA is considered acceptable.

- Computer systems access must be limited to authorized individuals: access is gained only after inputting a user name and a password. The system should require frequent changes of each individual password.
- A confirmation of the integrity and accuracy of the information stored in the system ~~must~~ should be completed.
- The operation of the system must be checked routinely to ensure that the correct information is transferred from the database to the printed record.
- Data entered into a database from which information is extracted for a COA ~~must~~ should be accompanied by time- and date-stamped audit trails.

When these criteria are met, the issuance of COAs with electronic signatures or the responsible person's name attached to the document, in lieu of a handwritten signature, is acceptable. [NOTE—Computer systems are currently regulated by 21 CFR 11 of the Food and Drug Administration (FDA). Users should monitor the FDA's approach to compliance in this area.]

DISTRIBUTOR INFORMATION

The presentation of a COA issued by a distributor presents some challenges. Because COAs are important documents characterizing the excipients and the state of their quality, the source of that information becomes very important to the end user(s). Because distributors take on different roles in fulfilling the services for which they are contracted, it is necessary to ensure that procedures and methods are appropriate for the functions performed.

Distributors may function in a number of different capacities relating to the movement of excipients and to services associated with their production. Some are simply pass-through locations in which nothing is done to the excipient with the exception of storage and handling. Others serve as extensions of the manufacturer's process by taking bulk quantities and repackaging them for the manufacturer. Still others purchase excipients and repackage them under a different label for sale and distribution. These scenarios ~~need to~~ should be understood and properly documented with programs that will protect the integrity and safety of the excipients as they move through the distribution process.

Original Manufacturer and Manufacturing Site—The identity of the original manufacturer and the manufacturing site ~~must~~ should be included on the COA for excipients. This information is important because it provides traceability for specific excipient lots and assures the excipient users that they are consistently obtaining material from the same manufacturer and site.

Reporting the identity and location of the manufacturer does not represent an issue when the original manufacturer is also the direct supplier of the excipient to the pharmaceutical customers. However, it is recognized that this information may be considered proprietary by an excipient distributor. To adequately address this issue, excipient distributors ~~must~~ should either list the specific information identifying the original manufacturer and location or provide the information by reporting an appropriate code, which is assigned in order to unambiguously identify the original manufacturer and manufacturing site. To protect the secrecy of this information, the meaning of the code does not have to be revealed to intermediary distributors.

Certificate of Analysis Data—When a distributor is primarily used as a pass-through of the excipient without any changes to the excipient and packaging, the COA that accompanies the excipient from the manufacturer can be passed on in the original form. If the data are extracted, translated, or rewritten on other letterhead, a system ~~must~~ should be in place to check the rewritten information, and justification should be demonstrated upon request. Alternatively, the source of the data should be indicated on the document.

For a distributor that takes bulk quantities of an excipient from a manufacturer and introduces the bulk quantities into a process (e.g., conveyance and storage system), analysis of the packaged excipient should be performed to demonstrate the same quality as the lot (batch) introduced. Appropriate analytical data should be included on the COA to verify the quality. The distributor ~~must~~ should use equivalent methodology and equipment for the analytical evaluation. Some data may be used from the original manufacturer's COA with appropriate justification.

In all scenarios, it is expected that the distributor will have the appropriate level of GMP in place.

APPENDIX 1

DEFINITIONS

Acceptance Criteria—The specifications and acceptance or rejection limits—such as acceptable quality level or unacceptable quality level with an associated sampling plan—

that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or excipient.

Batch (or Lot)—A defined quantity of excipient processed so that it could be expected to be homogeneous. In a continuous process, a batch corresponds to a defined portion of the production, based on time or quantity (e.g., vessel's volume, 1 day's production, etc.).

Batch Number (or Lot Number)—A unique and distinctive combination of numbers and/or letters from which the complete history of the manufacture, processing, packaging, coding, and distribution of a batch can be determined.

Batch Process—A manufacturing process that produces the excipient from a discrete supply of raw materials that is present before the completion of the reaction.

Certificate of Analysis (COA)—A document relating specifically to the results of testing a representative sample drawn from the batch of material to be delivered.

Chemical Property—A quality parameter that is measured by chemical or physicochemical test methods.

Continuous Process—A manufacturing process that continually produces the excipient from a continuous supply of raw material.

Contract Facility—An internal or external facility that provides services to the manufacturer or distributor of an excipient. These can include, but are not limited to, the following: manufacturing facilities, laboratories, repackaging facilities (including labeling), and warehouses.

Date of Manufacture—A date indicating the completion of the final manufacturing process (as defined by the supplier for the particular excipient and process).

Date Retested—The date when retesting is performed by an excipient supplier to extend the length of time that the material may be used.

Distributor—A party other than the manufacturer who sells the excipient.

Excipient—Any substance, other than the active pharmaceutical ingredient or drug product, that has been appropriately evaluated for safety and is included in a drug delivery system to aid the processing of the drug delivery system during manufacture; to protect, support, or enhance stability, bioavailability, or patient acceptability; to assist in product identification; or to enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Expiration Date—The date after which the supplier recommends that the material should not be used.

Impurity—Any component of an excipient that is not the intended chemical entity but is present as a consequence of either the raw materials used or the manufacturing process.

Lot—See *Batch*.

Lot Number—See *Batch Number*.

Manufacturer—A party who performs the final processing step.

Packaging—The container and its components that hold the excipient for storage and transport to the customer.

Periodic Testing Program—See *Skip-Lot Testing Program*.

Physical Property—A quality parameter that can be measured solely with mechanical equipment.

Process—The set of operating instructions describing how the excipient is to be synthesized, isolated, purified, etc.

Process Capability Index (*Cp*)—A statistical measurement that can be used to assess whether the process is adequate to meet specifications. A state of statistical control can be said to exist if the random variation in test results for a

process parameter is such that the calculated process capability is greater than 1.33 (see *Appendix 2* for further definition).

Process Step—An instruction to the excipient manufacturing personnel directing that an operation be done.

Recommended Re-Evaluation Date—The date suggested by the supplier when the material should be re-evaluated to ensure continued compliance with specifications. Differs from the *Expiration Date* in that the excipient may be re-evaluated to extend the length of time the material may be used, if supported by the results of the evaluation and appropriate stability data.

Reduced Frequency Testing Program—See *Skip-Lot Testing.*

Repackaging—Transfer of an excipient from one container to another.

Reprocessing—Introducing previously processed material that did not conform to standards or specifications back into the process and repeating steps that are already part of the normal manufacturing process.

Significant Change—Any change that alters an excipient's physical or chemical property from the norm or that is likely to alter the excipient's performance in the dosage form.

Site—A location where the excipient is manufactured. This may be within the facility but in a different operational area, or at a remote facility, including a contract manufacturer.

Skip-Lot Testing Program—Periodic or intermittent testing performed for a particular test parameter that is justified by historical data demonstrating a state of statistical process control.

Specification—The quality parameters to which the excipient, component, or intermediate must conform and that serve as a basis for quality evaluation.

Stable Process—A process whose output, regardless of the nature of the processing (batch or continuous), can be demonstrated by appropriate means to show a level of variability that consistently meets all aspects of the stated specification (both USP-specific and customer-specific) and is thus acceptable for its intended use.

Supplier—A manufacturer or distributor who directly provides the excipient to the user.

User—A party who uses an excipient in the manufacture of a drug product or another excipient.

APPENDIX 2

STATE OF STATISTICAL CONTROL: PROCESS CAPABILITY PARAMETERS FOR DETERMINING LEVELS OF CONTROL

A process is considered to be in a state of statistical control if variations among the observed sampling results from the process can be attributed to a constant system of chance causes. Process capability index (*Cp*) or capability index adjusted for the process average (*Cpk*) or performance index (*Pp*) or performance index adjusted for the process average (*Ppk*) can be used to assess whether the process is adequate to meet specifications. Values of these parameters exceeding 1.33 show that the process is adequate to meet specifications. Values between 1.00 and 1.33 indicate that the process, although adequate to meet specifications, will require close control. Values below 1.00 indicate that the process is not adequate to meet specifications and that the process and/or specifications ~~must~~ should be changed. *Pp/Ppk* will always be less than or equal to *Cp/Cpk*, respectively. The essential difference between the capability and the

performance indices is the data used. Capability indices require the calculation of σ, the population standard deviation, whereas the performance indices require the calculation of s, the sample standard deviation. Thus for pharmaceutical excipients a state of statistical control can be said to exist if the random variation in test results for a process parameter is such that the calculated process capability index or performance index is greater than 1.33.■2S (*USP29*)

BRIEFING

⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients, page 1662 of *PF* 28(5) [Sept.–Oct. 2002]. This proposed new general information chapter, which previously appeared in *Pharmacopeial Previews,* is now forwarded with editorial changes to *In-Process Revision.* The chapter is based on the *Significant Change Guide for Bulk Pharmaceutical Excipients,* prepared by the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas). The chapter defines the required elements of a significant change in process and will assist in establishing a uniform understanding of the roles and responsibilities of excipient manufacturers. This chapter, published with the permission of IPEC-Americas, is informational and contains no standards, tests, assays, or other mandatory specifications with respect to any Pharmacopeial article. On the basis of comments received, changes are added to the section *Change Risk Levels* to require customer notification for *Level 2* and *Level 3* changes.

(ETM: J. Lane) RTS—37804-1; 39717-1

Add the following:

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■⟨1195⟩ SIGNIFICANT CHANGE GUIDE FOR BULK PHARMACEUTICAL EXCIPIENTS

BACKGROUND

This general information chapter was derived from an international guidance on the evaluation of the significance of changes involving the manufacture of bulk pharmaceutical excipients. It is intended to assist excipient manufacturers in determining the need for informing the excipient customer and regulatory authorities about the nature of the change.

The principles and information in this chapter can be applied to the manufacture of all bulk pharmaceutical excipients (referred to throughout this document as "excipient[s]") intended for use in human drugs, veterinary drugs, and biologics. The principles set forth here must be applied from the point in the manufacturing process at which good manufacturing practices (GMPs) begin. The chapter provides minimum recommendations when considering the effect of a change on the excipient. When deciding how to use this chapter, each manufacturer must consider how it may apply to that manufacturer's product and processes. The diversity of excipients means that some principles of this chapter may not be applicable to certain products and processes.

This chapter is divided into several parts. The first part provides the general guidance necessary for evaluating a change and determining the necessity of informing the customer and/or regulatory authorities. One part provides criteria for determining whether a change will involve a significant risk. Also included is a decision tree that is useful in considering the potential effect of a change on excipient performance.

GENERAL GUIDANCE

International regulations governing drugs require that components of the drugs be manufactured, processed, packed, and held in accordance with GMPs. Unlike other pharmaceutical products and components, until now there has been no guidance that specifically addresses the manufacture of bulk pharmaceutical excipients. Evaluating the effect of a change in the manufacture of an excipient is more difficult than evaluating the effect of change for an active pharmaceutical ingredient (API). Whereas the API is seldom used for more than a handful of therapeutic purposes, the bulk pharmaceutical excipient is often used with a broad

range of active ingredients and in a diverse range of finished dosage forms. Whereas the API is typically of high purity and well characterized by the quality control and analytical laboratory, the bulk pharmaceutical excipient is often a natural substance or a mixture of polymers whose chemical and physical properties are more difficult to quantify.

SIGNIFICANT CHANGE

Any change by the manufacturer of an excipient that causes a physical or chemical property of the excipient to deviate from the norm or that is likely to alter the excipient's performance in the dosage form is considered significant. Such changes may necessitate notifying the local regulatory authority as required. Regardless of whether there is a regulatory requirement, the manufacturer has an obligation to notify its customers of a significant change so that the customer can evaluate the effect of the change on the customer's products. There are several types of change to be considered, as listed below.

- Site
- Scale
- Equipment
- Process
- Packaging
- Specification

The requirement for evaluating the effect of change on the excipient begins at the process step from which GMP compliance begins or at a step later in the process. It is important to give careful consideration to any processing changes after the excipient has been synthesized or isolated, but before packaging. It must be recognized that a change made earlier in the process can result in a change in excipient functionality. It is therefore recommended that earlier changes also be considered.

Evaluation Criteria

The six criteria to consider when evaluating the effect of a change in excipient manufacture are as follows:

1. Has there been a change in the chemical properties of the excipient as a result of the change?
2. Has there been a change in the physical properties of the excipient as a result of the change?
3. Has there been a change in the impurity profile of the excipient as a result of the change?
4. Has there been a change in the functionality of the excipient as a result of the change?
5. Where applicable, has the moisture level changed?
6. Where applicable, has the bioburden changed?

An affirmative answer to any of these questions indicates that the effect of the change on the excipient may lead to changes in its performance in the dosage form.

Determination of Significance

Chemical Properties—The evaluation of the chemical properties of an excipient must include, at a minimum, all monograph and manufacturer specification parameters. The excipient often contains moisture, the presence of which can have an effect on excipient performance in the preparation of the pharmaceutical dosage form. Therefore, a change in the moisture level, even within the compendial or specification limit, can affect the excipient's end use.

Physical Properties—A consideration of the physical properties of an excipient should be based on the physical form of the excipient and its functionality as used by the customers. Any physical property that is part of a mutually agreed specification between the manufacturer and customer should also be evaluated. For example, a manufacturer of an excipient powder should consider measuring the effect of changes on such physical parameters as bulk density, sur-

face area, particle shape, and particle size distribution. Liquid excipients might be evaluated for changes in pH and viscosity. For all polymeric excipients, the effect of the change on the molecular weight distribution should be considered.

Impurity Profile—Objective criteria are necessary when considering changes to the impurity profile for an excipient as a result of manufacture changes. A typical impurity profile contains the following:

- All specified organic impurities
- Unidentified organic impurities at or above 0.1%, whether specified or not
- Residual solvents
- Inorganic impurities
- Toxic impurities

Unidentified impurities should be monitored as part of the impurity profile if they are present at or above 0.1%, unless the impurity has an established pharmacological effect or is known to be unsafe at a lower level.

The content of the impurity profile varies with the nature of the excipient, the raw materials used in its manufacture, and its chemical composition. Changes are considered significant whenever a new impurity, identified or not, is introduced at a concentration of 0.1%, or when an impurity previously present at or above 0.1% disappears. Changes in the quantity of an existing impurity specified in a monograph and reported on the Certificate of Analysis (COA) (see the general information chapter *Bulk Pharmaceutical Excipients—Certificate of Analysis* ⟨1080⟩ for an in-depth explanation of the required elements of a Certificate of Analysis) should be treated as a chemical property for the purposes of this evaluation.

Functionality—Objective criteria for evaluating changes to excipient functionality are desirable. However, the nature of this type of study can vary broadly on the basis of the excipient, its application in the dosage form, and the capabilities of the excipient manufacturer. Therefore, this general information chapter cannot provide objective criteria for this study but stresses the importance of such a consideration by the manufacturer.

Bioburden—Change, especially in the processing steps or equipment, can adversely affect control of microorganisms in the excipient. Therefore, the effect of the change on the bioburden should be evaluated, particularly for excipients susceptible to microbial growth.

Change Risk Levels

In the evaluation of the effect of changes to the excipient, it is recognized that even with objective criteria some judgment may be necessary. To aid in the decision about the significance of a change and its likely effect on the dosage form, the types of changes are classified into three levels, as defined below.

Level 1: Minor—The changes are fairly minor and considered unlikely to affect the excipient chemical or physical properties, impurity profile, or functionality. Such changes should be documented, but notification to the customer is not necessary.

Level 2: Might be Significant—The effect of the change should be evaluated against criteria 1, 2, and 3 (chemical properties, physical properties, and impurity profile) in the *Evaluation Criteria* subsection, to determine its potential effect on excipient functionality. ~~Notification of these types of changes to the customer is strongly suggested. However, pre-approval by the user is not normally needed unless it is shown that functionality is affected.~~ This type of change should always be communicated to the customer.

Level 3: Always Significant—~~Unless there is a sound basis for concluding the change does not impact excipient functionality, notification to the customer is strongly recommended.~~ This type of change should always be communi-

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cated to the customer. Shipment of the changed excipient to the customer should not occur without consent from the user company.

Protocol Design

There should be a written protocol for the evaluation of a change to determine whether it is significant. The protocol should describe the nature of the change, the reason it may be significant, the testing to be performed to evaluate the change, and the criteria for determining the significance. The use of a minimum of three lots each of the pre- and postchange excipient is recommended for confirmation testing.

After a change has been made, the manufacturer should test the excipient for all specification properties and compare the results to the historical data. It is suggested that standard statistical tests be used to compare the average of the new data with the average of the historical data. If these averages are different at the 95% statistical confidence level, the change is considered significant. As a further check on consistency, it is also recommended that the new batch-specification properties be plotted on standard statistical quality control (SQC) charts, along with standard batch results.

Supporting Data

It is preferable to use data to measure the effect of a change on the excipient. When sufficient material exists, an acceptable evaluation should include the comparison of 3 batches of material made after the change with 10 batches manufactured before the change. It is suggested that the comparison proceed beginning with chemical and physical properties, followed where appropriate by moisture, bioburden, impurity profile, and functionality. The manufacturer should use good judgment on sample comparisons for the other evaluation.

Chemical and physical properties lend themselves to quantitative measurement. These properties are often part of the specification for the excipient. Therefore, there should be a large body of test data for the properties that might be affected by a change to compare with the corresponding data for the excipient made after the change.

Equivalence of impurity profiles is shown by tabulating the data for the prechange and postchange lots. If the following conditions are met, there has been no significant change in the impurity profile.

1. No new impurity is present at or above 0.1%, and no impurity previously present in the impurity profile at this level has disappeared.
2. Residual solvent and impurities remain within three standard deviations of the mean of the lots produced before the change.
3. All impurities are at or below the mean plus three standard deviations of the lots produced before the change.

Types of Changes

Site—A change in site can involve either the production or the packaging of the excipient or its quality control testing. If the proposed manufacturing site was never used to produce the excipient, the change poses a great risk of altering the excipient performance and is considered a *Level 3* change. If the proposed site was used to produce excipients within the past year and the process, equipment, utilities, and raw materials are all unchanged, the risk is considered minor and thus a *Level 1* change. However, if the excipient was produced more than a year ago at the proposed site with the same process, equipment, utilities, and raw materials, the risk is a moderate, or *Level 2*, change.

If the change involves the quality control laboratory, then the effect hinges on the test method. If the method remains the same, the change is designated a *Level 1* change, assum-

ing that method validation is conducted. If the new laboratory uses a different analytical technique or analytical equipment, the change should be evaluated more carefully, as required for *Level 2*.

Scale—Manufacturers often find ways to increase the scale of production. If the excipient is being scaled up from pilot to production, the change is likely to be significant and thus would generate a *Level 3* change. When the change in scale results from the use of new and larger, or smaller, production equipment using the same operating principle (often the case in batch processing), the change is considered *Level 2*. If the existing equipment is optimized to increase capacity without altering the process (often found in continuous processing), the change is considered minor and treated as *Level 1*. However, careful consideration must be given to changes that can clearly affect the physical properties of the excipient.

Equipment—The evaluation of equipment changes involves the issue of equipment equivalence. Generally, equipment that is a replacement in kind is considered a minor *(Level 1)* change. If the new equipment is not a replacement in kind, but is included in the process validation, the change is still considered *Level 1*. Otherwise, the change is considered *Level 3*.

Process—A change in process often involves changes to the processing instructions such as target levels for such parameters as temperature, pressure, and flow rate; the raw materials to be used; the sequence of operating steps; and the operation to be performed, including reprocessing. As illustrated in the decision tree in *Appendix 2,* each type of process change can be further detailed.

If there is a change in a process parameter that is included in the process validation, such as operating at a new target within the qualified range, it is a *Level 1* change. However, if the process parameter is outside the validation, the change must be evaluated as a *Level 2* change.

If minor changes are made to the processing steps, such as a small change in the rate of addition of an ingredient that falls outside the validated range, the change is considered *Level 2*. A major change, such as changing the point at which an ingredient is added—earlier or later in the process—is potentially significant, and thus *Level 3* would be appropriate.

The reprocessing of an excipient, followed by a purification step, when not typical of the process, should be evaluated as a *Level 2* change. However, if no further purification of the bulk excipient occurs, this type of change is considered *Level 3*.

Differences in raw materials can also be caused by a different supplier, that supplier's specifications, or the addition or removal of the raw material from the bulk pharmaceutical excipient process. If the new supplier provides a raw material that has essentially the same specification as the former supplier, and the raw material method of manufacture is similar, the change is minor and treated as *Level 1*. However, if there is a difference in either the specifications or the manufacturing process, the change must be evaluated as potentially significant *(Level 2)*. Finally, if the raw material change involves the addition or removal of an ingredient from the process for producing or preserving the excipient, or is otherwise used to produce the bulk excipient, the change is likely to be significant *(Level 3)*.

Packaging—These changes involve the package components for the protection and distribution of the excipient. Any change in the package or packaging components (such as the drum, box, liner, or tamper-evident seal), that is a replacement in kind is a minor *(Level 1)* change. Replacement in kind applies to containers constructed of the same materials and sealed in a similar manner, and to liners made of the same components. Any change that is not a replacement in kind should be evaluated as *Level 3*.

Specifications—Changes are sometimes made to the excipient specification or to the quality control test method. When changes are not the result of a monograph change, their significance must be evaluated. Such test or specification changes may be made to the excipient product or to an intermediate component.

Any change to an excipient specification or test method that is used to improve its quality is a *Level 3* change. For example, adding a new specification parameter for the purpose of improving the quality of the excipient through lot selection is a potentially very significant *Level 3* change. If the specification change relaxes a specification parameter, the effect on the excipient quality should be evaluated as a *Level 2* change. The additional testing of the excipient, initiated with the sole purpose of further characterizing the material without altering its quality, is a minor, low-risk, *Level 1* change.

If a specification for a raw material from the same supplier(s) is made more stringent, the change is unlikely to be significant *(Level 1)*, whereas if the specification is made less stringent, the change should be evaluated more carefully *(Level 2)*.

When a change is made that either increases or maintains the level of process control in the manufacturing process, it should be treated as a *Level 1* change. If the change in process control relaxes the control, the effect should be carefully evaluated as a *Level 2* change. An illustrative example is pH control. If a new pH meter allows for more precise measurement, the process control is improved and the change falls under *Level 1*. However, if the pH control is relaxed through the use of a less precise measuring device, the change falls under *Level 2*.

Multiple Changes—Such changes involve more than one change occurring simultaneously. The risk level that governs consideration of the effect of the changes should be the highest level for any single change.

Reporting Requirements

Documentation—It is recommended that the evaluation of all changes to the excipient be documented regardless of the level of change. The report should indicate the basis for evaluating the effect of the change on the excipient, the data used in reaching the conclusion as to its significance, and the actions taken.

Where appropriate, the process validation should be updated to reflect the changed process. This is clearly indicated when the evaluation has led to the conclusion that the change should be considered significant.

Notification—The customer should be given as much advance notification of impending change as possible. For *Level 3* changes in particular, the customer may require time to complete the evaluation of the effect of the change on the customer's formulations. During this period the customer may request inventory of the excipient produced before the change was made. The manufacturer should plan for the change with this eventuality in mind.

Regardless of the apparent level of the change, all changes that, upon evaluation, are found to meet the definition of significant change require customer notification.

Regulatory authorities often require notification of significant changes involving the manufacture of excipients. Such notification should be made as required by applicable authority.

APPENDIX 1. DEFINITIONS

Active Pharmaceutical Ingredient: a substance that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals.

Batch Process: a manufacturing process that produces the excipient from a discrete supply of the raw materials that are present before the completion of the reaction.

Bioburden: the nature and quantity of microorganisms present in the excipient.

Chemical Property: a quality parameter that is measured by chemical or physicochemical test methods.

Confidence Level: a range, calculated from sample data, within which a population parameter, such as the population mean, is expected to lie, with a given level of confidence.

Continuous Process: a manufacturing process that continually produces the excipient from a continuous supply of raw material.

Decision Tree: a visual presentation of the sequence of events that can occur, including decision points.

Equipment: the implements used in the manufacture of an excipient.

Excipient: any substance, other than the active drug or product, that has been appropriately evaluated for safety and is included in a drug delivery system to either aid the processing of the drug delivery system during manufacture; protect, support, or enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

Functionality: the set of performance criteria that the excipient is intended to meet.

Impurity: any component of an excipient that is not the intended chemical entity but is present as a consequence of either the raw materials used or the manufacturing process.

Impurity Profile: a description of all of the impurities present in the excipient.

Packaging: the container and its components that hold the excipient for transport to the customer.

Pharmacological Effect: any therapeutic effect.

Physical Property: a quality parameter that can be measured solely with mechanical equipment.

Process: the set of operating instructions describing how the excipient is to be synthesized, isolated, purified, packaged, etc.

Process Parameter: a measurable operating condition.

Process Step: an instruction to the bulk pharmaceutical excipient manufacturing personnel directing that an operation be done.

Reprocessing: introducing previously processed material that did not conform to standards or specifications back into the process and repeating steps that are already part of the normal manufacturing process.

Replacement in Kind: manufacturing equipment that uses the same operating principle and is of similar construction. Packaging components made with the same materials of construction and sealed in a similar manner.

Scale: an increase or decrease in the batch size, whether or not different equipment is used.

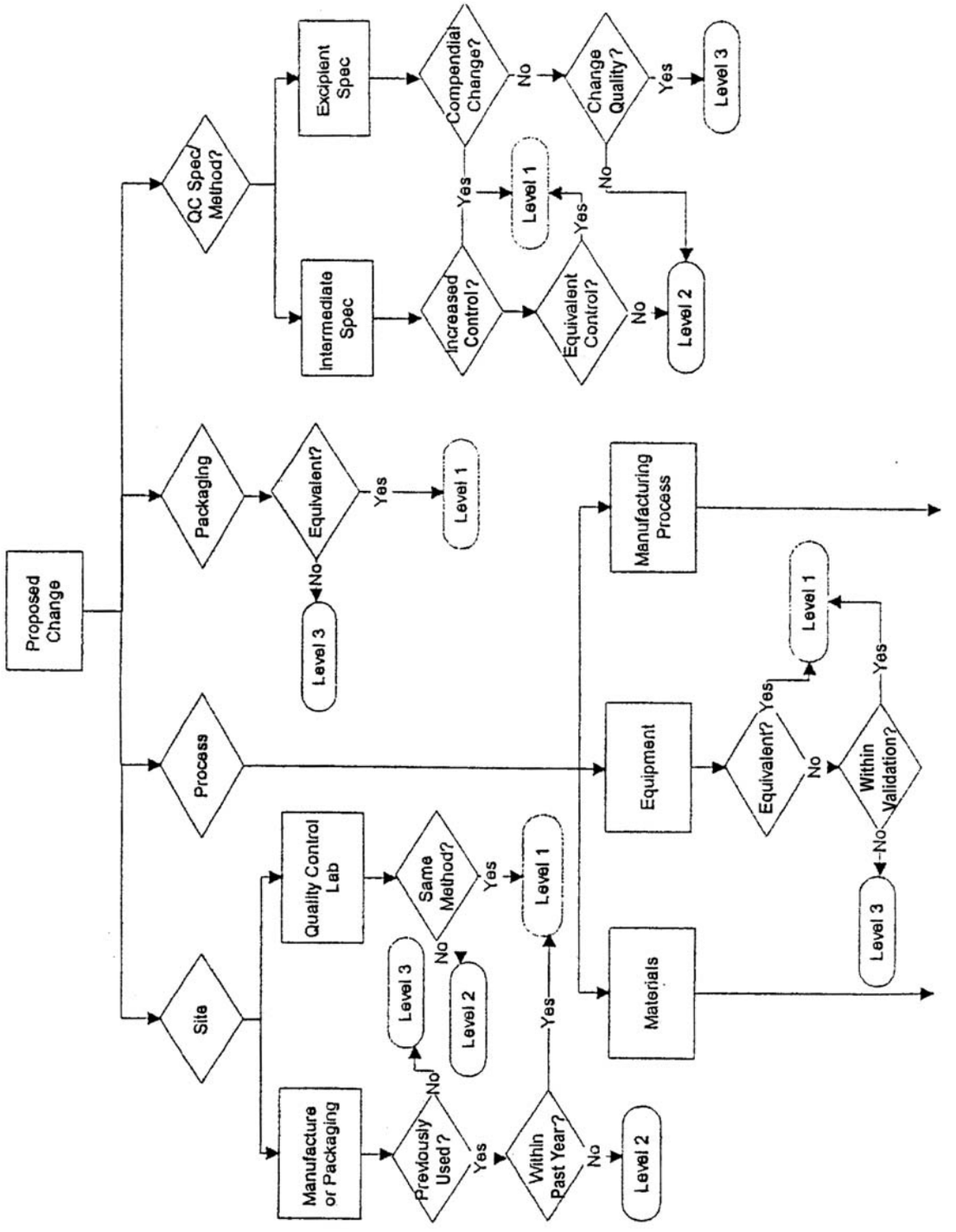
Site: a location where the excipient is manufactured; may be within the facility but in a different operational area or at a remote facility, including a contract manufacturer.

Significant Change: any change that causes a physical or chemical property of the excipient to deviate from the norm or that is likely to alter the excipient's performance in the dosage form.

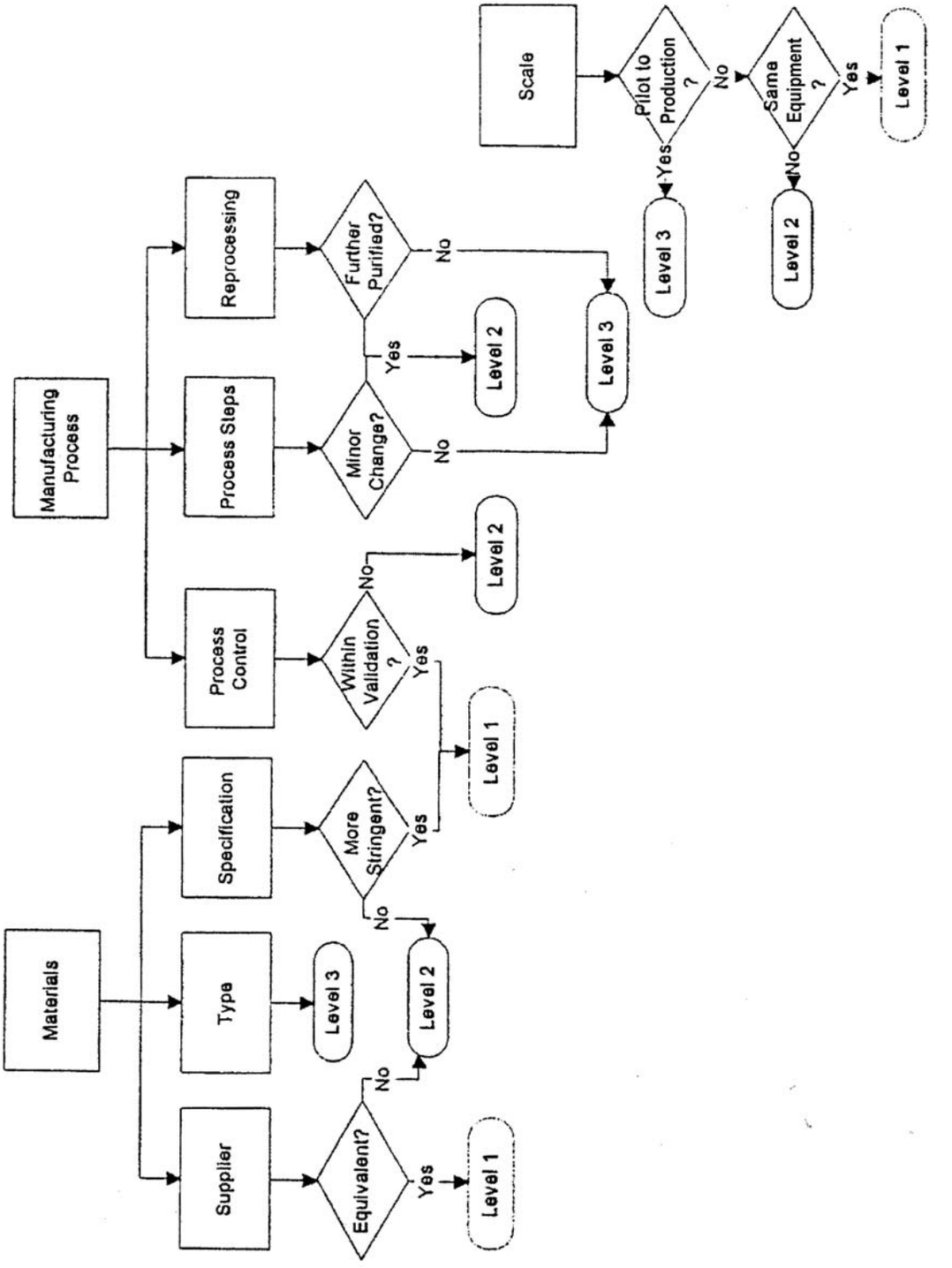
Specification: the quality parameters to which the excipient, component, or intermediate component must conform and that serve as a basis for quality evaluation.

Toxic Impurity: impurities known to have significant undesirable biological activity.

APPENDIX 2. Decision Tree



APPENDIX 2. Decision Tree *(continued)*



REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

3-Aminopropionic Acid, *USP 28* page 2798. It is proposed to include chemical information to facilitate the procurement of this reagent.

(HDQ: M. Marques) RTS—42531-1

Change to read:

3-Aminopropionic Acid~~— See *β-Alanine*~~

■(*β-Alanine),* $NH_2CH_2CH_2COOH$—**89.09** [*107-95-9*]—Use a suitable grade.■2S (*USP29*)

BRIEFING

1-Butaneboronic Acid, *USP 28* page 2804. It is proposed to delete this reagent because of its redundancy. It is a synonym of *n-Butylboronic Acid.*

(HDQ: M. Marques) RTS—42489-1

Delete the following:

~~■**1-Butaneboronic Acid,** $C_4H_{11}BO_2$— **101.94** — White flakes.~~

~~*Assay*— Dissolve about 50 mg, accurately weighed, in 2 mL of bis(trimethylsilyl)acetamide, and mix while heating to boiling. Allow the solution to cool, and 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 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the $C_4H_{11}BO_2$ peak is not less than 99% of the total peak area.~~

~~*Solubility*— A solution of 50 mg in 1 mL of alcohol is clear and colorless.~~

~~*Melting range* ⟨741⟩: — between 92° and 95°.~~■2S (*USP29*)

BRIEFING

Butyl Methacrylate. This new reagent is specified in the test for *Limit of monomers, Test 1* under *Amino Methacrylate Copolymer.*

(HDQ: M. Marques) RTS—39405-1; 40243-1

Add the following:

■**Butyl Methacrylate,** $C_8H_{14}O_2$—**142.20** [*97-88-1*]—Use a suitable grade.■2S (*USP29*)

BRIEFING

***n*-Butylboronic Acid,** *USP 28* page 2805. It is proposed to add the synonym and CAS number for this reagent to facilitate its procurement.

(HDQ: M. Marques) RTS—42489-1

Change to read:

***n*-Butylboronic Acid**

■(*1-Butaneboronic Acid*),■2S (*USP29*)
$C_4H_9B(OH)_2$—**101.94**

■[*4426-47-5*]■2S (*USP29*)
—Use a suitable grade.
[NOTE—This reagent is usually shipped and stored under water. Before use, remove any excess water by light vacuum filtration. A suitable grade is available from Sigma-Aldrich, www.sigma-aldrich.com.]

In-Process Revision

BRIEFING

2-Dimethylaminoethyl Methacrylate. This new reagent is specified in the test for *Limit of monomers, Test 2* under *Amino Methacrylate Copolymer.*

(HDQ: M. Marques) RTS—39405-1; 40243-1

Add the following:

■**2-Dimethylaminoethyl Methacrylate,** $H_2C = CHCO_2CH_2CH_2N(CH_3)_2$—**143.18** [*2439-35-2*]—Use a suitable grade.■2S (*USP29*)

BRIEFING

Docusate Sodium. This new reagent is used in the test for *Content of benzalkonium chloride* in the proposed new monograph for *Fluticasone Propionate Nasal Spray,* appearing elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41571-3

Add the following:

■**Docusate Sodium**—Use *Docusate Sodium* (USP monograph).■2S (*USP29*)

BRIEFING

Furfural, *USP 28* page 2820. It is proposed to harmonize the specifications for this reagent with the American Chemical Society Reagents Specifications.

(HDQ: M. Marques) RTS—42539-1

Change to read:

Furfural

■(*2-Furancarboxyaldehyde, 2-Furaldehyde*),■2S (*USP29*) C_4H_3OCHO—**96.08**

■[*98-01-1*]■2S (*USP29*)

~~—A clear, colorless liquid when freshly distilled, but soon turns reddish brown. Soluble in water. Miscible with alcohol. Store in tight, light-resistant containers. Before use it should be freshly distilled.~~

~~*Boiling range*—(Reagent test)—Not less than 95% distils between 159° and 162°.~~

■Use ACS reagent grade.■2S (*USP29*)

BRIEFING

Thioglycolic Acid, *USP 28* page 2846 and page 587 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to review the specifications for this reagent in order to be in accordance with the products currently available on the market.

(HDQ: M. Marques) RTS—42540-1

Change to read:

Thioglycolic Acid, ~~(*Thioglycolic Acid*)~~

■■2S (*USP29*)
$HSCH_2COOH$—**92.12**

■[*68-11-1*]■2S (*USP29*)
—A colorless or nearly colorless liquid. ~~having a strong, unpleasant odor.~~

▲▲*USP29*
Miscible with water. Soluble in alcohol.

~~*Residue on ignition*—(Reagent test)—not more than 0.1%.~~

~~*Solubility*—A solution of 1 mL in 10 mL of water is clear and colorless.~~

■■2S (*USP29*)
Sensitiveness—Mix 1 mL with 2 mL of stronger ammonia water, and dilute with water to 20 mL. Add 1 mL of this solution to a mixture of 20 mL of water and 0.1 mL of dilute ferric chloride TS (1 in 100), then add 5 mL of ammonia TS: a distinct pink color is produced.

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869, page 3346 of the *First Supplement,* and page 859 of *PF* 31(3) [May–June 2005].

(HDQ) RTS—41546-2; 41809-1; 41818-2; 41818-5; 41818-6; 41818-7

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:	
▲Benazepril Tablets	W ▲*USP29*
Add the following:	
■Bismuth Subsalicylate Tablets	T ■2S (*USP28*)
Add the following:	
■Cefaclor Tablets	T ■2S (*USP28*)
Add the following:	
■Chromium Picolinate Tablets	W ■2S (*USP28*)
Add the following:	
■Citalopram ~~Hydrobromide~~ Tablets	W ■1S (*USP29*)
Add the following:	
■Clarithromycin Tablets, Extended-Release	W ■2S (*USP28*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
▲Black Cohosh Tablets	T, LR ▲*USP29*
Add the following:	
▲Desogestrel and Ethinyl Estradiol Tablets	W ▲*USP29*
Add the following:	
▲Estradiol and Norethindrone Acetate Tablets	W ▲*USP29*
Add the following:	
▲Fexofenadine Hydrochloride Tablets	W ▲*USP29*
Add the following:	
▲Fosinopril Sodium Tablets	T ▲*USP29*
Add the following:	
▲Fosinopril Sodium and Hydrochlorothiazide Tablets	T ▲*USP29*
Add the following:	
■Gabapentin Capsules	W ■2S (*USP28*)
Add the following:	
▲Ginkgo Capsules	T, LR ▲*USP29*
Add the following:	
▲Ginkgo Tablets	T, LR ▲*USP29*
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■ ■2S (*USP28*)
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR ■1S (*USP29*)
Add the following:	
▲Indinavir Sulfate Capsules	T ▲*USP29*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
▲Irbesartan Tablets	W▲*USP29*
Add the following:	
▲Irbesartan and Hydrochlorothiazide Tablets	W▲*USP29*
Add the following:	
▲Isosorbide Mononitrate Tablets	T▲*USP29*
Add the following:	
▲Isosorbide Mononitrate Tablets, Extended-Release	T▲*USP29*
Add the following:	
■Lysine Hydrochloride Tablets	W■2S *(USP28)*
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S *(USP29)*
Add the following:	
▲Modafinil Tablets	T▲*USP29*
Add the following:	
■Nefazodone Hydrochloride Tablets	T■2S *(USP29)*
Add the following:	
▲Norgestimate and Ethinyl Estradiol Tablets	W▲*USP29*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Omeprazole Capsules, Delayed-Release	T, LR■2S *(USP28)*
Add the following:	
■Oxaprozin Tablets	T, LR■2S *(USP28)*
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■2S *(USP29)*
Add the following:	
▲Quinapril Tablets	W▲*USP29*
Add the following:	
▲Tizanidine Tablets	T▲*USP29*
Add the following:	
▲Valerian Capsules	T, LR▲*USP29*
Add the following:	
▲Valsartan and Hydrochlorothiazide Tablets	W▲*USP29*
Add the following:	
▲Zinc Sulfate Tablets	W▲*USP29*

In-Process Revision

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 3347 of the *First Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1), [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 2057 of *PF* 29(6) [Nov.–Dec. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], and page 861 of *PF* 31(3) [May–June 2005].

(HDQ) RTS—33667-1; 38378-5; 39405-1; 40243-1; 40762-1; 41017-1; 41201-1; 41750-1; 41818-1; 41818-3; 41818-4; 41979-1; 41979-2; 42060-1; 42082-1; 42082-2; 42601-1

Add the following:

■**Amino Methacrylate Copolymer:** Colorless to yellowish granules. Soluble in acetone, in isopropyl alcohol, and in diluted acids; practically insoluble in water. The solutions are clear to slightly cloudy. *NF category:* Coating agent; polymer membrane; tablet binder.■2S (*NF24*)

Add the following:

■**Desmopressin Acetate:** White, fluffy powder. Soluble in water, in alcohol, and in acetic acid.■2S (*USP29*)

Add the following:

■**Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion:** Milky-white liquid of low viscosity with a faint, characteristic odor. It is miscible with water in any proportion; the milky-white appearance is retained. A clear or slightly opalescent, viscous solution is obtained on mixing one part with five parts of acetone, alcohol, or isopropyl alcohol; the polymer substance first precipitates, but then dissolves in the excess organic solvent. When mixed with 1 N sodium hydroxide in a ratio of 1 : 2, the dispersion does not dissolve; the milky-white appearance is retained. *NF category:* Coating agent; polymer membrane; tablet binder.■2S (*NF24*)

Change to read:

Hyoscyamine Sulfate: White~~, odorless crystals or crystalline powder.~~

■or almost white crystalline powder or colorless needles.■2S (*USP29*)
Is deliquescent and is affected by light. The pH of a solution (1 in 100) is about 5.3. Very soluble in water; freely soluble in alcohol; practically insoluble in ether.

■Melts at a temperature not less than 200°.■2S (*USP29*)

Change to read:

Loperamide Hydrochloride: White to slightly yellow powder. Melts at about 225°, with some decomposition. Freely soluble in methanol~~, in isopropyl alcohol,~~

■■2S (*USP29*)
and in chloroform; slightly soluble in water and in dilute acids;

■very slightly soluble in isopropyl alcohol.■2S (*USP29*)

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.~~

■or relatively dense, white powder or granulated powder.■2S (*USP29*)
Soluble in dilute acids; practically insoluble in water; insoluble in alcohol.

Add the following:

■**Maltitol:** White, crystalline powder. Very soluble in water; practically insoluble in ethanol. *NF Category:* Humectant; sweetening agent; tablet and/or capsule diluent.■2S (*NF24*)

Add the following:

■**Nefazodone Hydrochloride:** Nonhygroscopic, white powder. Freely soluble in chloroform; soluble in propylene glycol; slightly soluble in polyethylene glycol and in water.■2S (*USP29*)

Add the following:

■**Pamidronate Disodium:** White, crystalline powder. Soluble in water and in 2 N sodium hydroxide; sparingly soluble in 0.1 N hydrochloric acid and in 0.1 N acetic acid; practically insoluble in organic solvents.■2S (*USP29*)

Add the following:

■**Tazobactam:** White to pale yellow, nonhygroscopic, crystalline powder. Soluble in dimethylformamide; moderately soluble in water, in methanol, in acetone, and in ethanol; slightly soluble in ethyl acetate, in ethyl ether, and in chloroform; insoluble in hexane.■2S (*USP29*)

Add the following:

■**Travoprost:** Clear, colorless, viscous oil. Insoluble in water.■2S (*USP29*)

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF.* For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 31(1) through 31(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

Title and Proposal	***PF Volume, Issue, and Page Numbers of Pending Proposals***		
	Vol.	***No.***	***Page(s)***
General Notices—*Tests and Assays—Residual Solvents (delayed implementation to January 1, 2007); Preservation, Packaging, Storage, and Labeling—Poison Prevention Packaging Act; Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs*	31	3	718
USP Monographs			
Acetaminophen Oral Suspension—*USP Reference standards [USP 4-Aminophenol RS]* (add), *Limit of 4-aminophenol* (add)	30	5	1579
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid—*Limit of hydroxylamine*	30	5	1579
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Acetylcysteine—*USP Reference standards, Assay*	31	3	726

Pending Proposals (*continued*)

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

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Acyclovir—*Assay and limit for guanine*	30	5	1580
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albumin Human—*Definition, Expiration date, USP Reference standards,* (add), *Identification A, B* (add), *pH* (add), *Molecular size distribution* (add), *Prekallikrein activator* (add), *Protein content*(add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add), *Packaging and storage, Labeling, Bacterial endotoxins* (add), *Sterility* (add), *Heat sterility* (add), *Safety* (add)	29	4	992
Albuterol Tablets—*Dissolution, Assay*	31	3	726
Alcohol (new)—*Harmonization*	30	5	1844
Dehydrated Alcohol (new)—*Harmonization*	30	5	1848
Alcohol in Dextrose Injection—*Assay for dextrose*	30	5	1581
Allopurinol—*USP Reference standards, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	28	5	1386
Alprazolam Tablets—*Identification, Dissolution*	30	5	1582
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Amifostine—*Related compounds*	30	6	1974
Amifostine for Injection—*Related compounds*	30	6	1976
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amoxicillin Capsules—*Dissolution*	30	5	1583
Amoxicillin Tablets—*Dissolution*	30	6	1977
Amphetamine Sulfate—*Assay*	31	2	381
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Anticoagulant Citrate Dextrose Solution—*USP Reference standards (delayed implementation to April 1, 2009), Assay for total citrate (delayed implementation to April 1, 2009), Assay for dextrose*	31	3	727
Anticoagulant Citrate Phosphate Dextrose Adenine Solution—*USP Reference standards (delayed implementation to April 1, 2009), Assay for total citrate* (delete) *(delayed implementation to April 1, 2009), Assay for total phosphate* (delete) *(delayed implementation to April 1, 2009), Assay for total citrate and total phosphate* (add) *(delayed implementation to April 1, 2009)*	31	3	728
Anticoagulant Citrate Phosphate Dextrose Solution—*USP Reference standards (delayed implementation to April 1, 2009), Assay for total citrate* (delete) *(delayed implementation to April 1, 2009), Assay for total phosphate* (delete) *(delayed implementation to April 1, 2009), Assay for total citrate and total phosphate* (add) *(delayed implementation to April 1, 2009)*	31	3	730
Anticoagulant Sodium Citrate Solution—*USP Reference standards (delayed implementation to April 1, 2009), Assay (delayed implementation to April 1, 2009)*	31	3	731
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Tablets—*Dissolution*	30	1	61
Benazepril Hydrochloride (new)	29	5	1422
Benazepril Hydrochloride Tablets (new)	29	3	606

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Betahistine Hydrochloride (new)	30	5	1584
Betamethasone Acetate—*Identification B*	31	2	381
Betamethasone Tablets—*Dissolution*	30	1	62
Bethanechol Chloride—*Related compounds, Assay*	30	5	1586
Bethanechol Chloride Tablets—*Related compounds, Assay*	30	5	1587
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Bismuth Subsalicylate Oral Suspension (new)	30	4	1166
Bismuth Subsalicylate Tablets (new)	31	3	741
Bretylium Tosylate in Dextrose Injection—*Assay for dextrose*	30	5	1589
Brompheniramine Maleate Tablets—*Dissolution*	30	6	1978
Budesonide (new)	30	6	1978
Bupivacaine Hydrochloride—*Limit of residual solvents*	30	5	1589
Bupivacaine Hydrochloride in Dextrose Injection—*Assay for dextrose*	30	5	1590
Bupropion Hydrochloride—*Chromatographic purity*	31	2	381
Bupropion Hydrochloride Extended-Release Tablets—*USP Reference standards, Related compounds*	31	2	384
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Caffeine Citrate Injection—*Definition, Related compounds, Assay*	30	5	1590
Caffeine Citrate Oral Solution—*Definition, Related compounds, Assay*	30	5	1593
Calcitonin Salmon (new)	31	2	385
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	29	5	1433
Calcitriol Injection (new)	29	5	1434
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Camphor—*Water*	31	3	742
Carboxymethylcellulose Sodium Suspension (new)	30	3	812
Cefaclor Tablets (new)	29	6	1858
Cefaclor Extended-Release Tablets—*Labeling* (delete)	31	1	42
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Ciclopirox Olamine Cream—*USP Reference standards [USP Benzyl Alcohol RS], Content of benzyl alcohol*	30	5	1595
Ciclopirox Olamine Topical Suspension—*USP Reference standards [USP Benzyl Alcohol RS]*	30	5	1596
Ciprofloxacin—*USP Reference standards, Other requirements*	31	2	393
Ciprofloxacin Injection—*Definition, USP Reference standards, Pyrogen* (delete), *Bacterial endotoxins* (add), *Limit of ciprofloxacin ethylene diamine analog, Dextrose content*	31	2	393
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	3	745
Anhydrous Citric Acid *(Harmonization)—Packaging and storage* (add), *Sulfate, Organic volatile impurities* (delete)	31	3	749
Citric Acid Monohydrate *(Harmonization)—Packaging and storage* (add), *Color of solution, Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid*	31	2	394
Cladribine (new)	31	2	395

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Clarithromycin—*Definition, USP Reference standards, Identification, Specific rotation, pH, Residue on ignition, Heavy metals, Related substances* (add), *Assay*	30	4	1179
Clarithromycin Tablets—*Assay*	30	4	1182
Clarithromycin Extended-Release Tablets (new)	30	4	1183
Clindamycin Injection—*USP Reference standards [USP Benzyl Alcohol RS], Assay*	30	5	1597
Clorazepate Dipotassium—*USP Reference standards, Related compounds*	30	6	1982
Clotrimazole Lozenges—*Disintegration* (delete), *Dissolution* (add)	31	2	398
Clozapine—*Chromatographic purity*	30	6	1984
Codeine Phosphate—*Packaging and storage*	30	5	1597
Colchicine Tablets—*Dissolution*	30	1	91
Cyclandelate (new)	30	6	1985
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Cysteine Hydrochloride—*Assay*	30	5	1598
Dalteparin Sodium (new)	30	5	1598
Dapsone—*Assay*	31	3	750
Cryopreserved Human Fibroblast-Derived Dermal Substitute (new)	30	4	1211
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Elixir (delete monograph)	30	5	1612
Dextroamphetamine Sulfate Oral Solution (delete monograph)	30	5	1643
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Dextrose Injection—*Assay*	30	5	1614
Dextrose and Sodium Chloride Injection—*Assay for dextrose*	30	5	1614
Dibucaine—*Identification B*	31	2	399
Dibucaine Cream—*Identification, Assay*	31	2	399
Dibucaine Ointment—*Identification*	31	2	400
Dibucaine Hydrochloride—*Labeling* (add), *USP Reference standards, Identification B, Other requirements* (add)	31	2	400
Dibucaine Hydrochloride Injection—*Identification A*	31	2	401
Diclofenac Sodium Delayed-Release Tablets—*Identification, Drug release, Dissolution (delayed implementation to April 1, 2006)*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add), *Assay*	29	6	1870
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Extended-Release Capsules—*Drug release, Test 14*	30	2	478
Dimercaprol Injection—*USP Reference standards* (add), *Bacterial endotoxins* (add)	30	6	1987
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Uniformity of dosage units*	30	6	1987
Dobutamine in Dextrose Injection—*Assay for dextrose*	30	5	1615
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dopamine Hydrochloride and Dextrose Injection—*Assay for dextrose*	30	5	1615
Dorzolamide Hydrochloride—*Limit of dorzolamide hydrochloride related compound A, Assay*	31	2	401
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride Capsules—*Identification*	30	6	1987
Drospirenone (new)	31	3	754

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Dyclonine Hydrochloride—*Identification B*	31	1	42
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Egg Phospholipids (new)	31	3	757
Multiple Electrolytes Injection Type 2—*USP Reference standards (delayed implementation to April 1, 2009), Assay for citrate (delayed implementation to April 1, 2009)*	31	3	759
Multiple Electrolytes and Dextrose Injection Type 1—*Assay for dextrose*	30	5	1616
Multiple Electrolytes and Dextrose Injection Type 2—*USP Reference standards (delayed implementation to April 1, 2009), Assay for citrate (delayed implementation to April 1, 2009)*	31	3	760
Enalapril Maleate and Hydrochlorothiazide Tablets—*Dissolution*	30	6	1988
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Epinephrine Injection—*Identification A, B*	31	1	43
Ergotamine Tartrate and Caffeine Suppositories—*Identification B*	30	6	1988
Ergotamine Tartrate and Caffeine Tablets—*Identification B*	30	6	1988
Estradiol and Norethindrone Acetate Tablets (new)	30	6	1989
Estradiol Transdermal System (new)	30	4	1201
Conjugated Estrogens—*Definition*	30	3	840
Ethacrynic Acid Tablets—*Dissolution*	30	6	1993
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102
Etidronate Disodium—*USP Reference standards [USP Etidronate Disodium Related Compound A RS], Limit of phosphite, Assay*	30	5	1616
Etidronate Disodium Tablets—*Dissolution, Assay*	30	5	1619
Famotidine for Oral Suspension (new)	30	6	1993
Famotidine Tablets—*Related compounds, Assay*	30	6	1995
Fenofibrate (new)	31	3	763
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Finasteride Tablets—*Dissolution*	30	5	1620
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Related compounds*	31	2	408
Flucytosine—*Fluorouracil*	30	5	1621
Fludarabine Phosphate—*Chloride, Assay*	30	5	1621
Fluoxetine Delayed-Release Capsules (new)	30	3	849
Flurazepam Hydrochloride—*Identification*	31	3	766
Fluvastatin Capsules (new)	31	1	47
Fluvastatin Sodium (new)	31	1	43
Fluvoxamine Maleate Tablets (new)	30	5	1622
Fosinopril Sodium (new)	30	6	2001
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Gabapentin Capsules (new)	28	7	298
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Dissolution*	30	1	105
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	2	410
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Helium—*USP Reference standards* and *Assay* (postponed indefinitely)	31	3	707
Hydrocodone Bitartrate—*USP Reference standards [USP Hydrocodone Bitartrate Related Compound A RS], Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109

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Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydrogen Peroxide Concentrate—*Acidity*	30	5	1629
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Indocyanine Green—*Definition, Assay*	29	6	1905
Insulin Human Injection—*Limit of high molecular weight proteins* (add), *Other requirements*	30	5	1630
Iodixanol—*Labeling* (add), *USP Reference standards, Limit of calcium, Other requirements* (add)	31	1	54
Irbesartan Tablets (new)	29	4	1035
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
Diluted Isosorbide Mononitrate (new)	30	3	868
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	30	3	871
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Ketoprofen—*Assay*	31	3	772
Lamivudine—*Limit of lamivudine enantiomer, Resolution solution, Limit of residual solvents*	30	3	881
Lansoprazole—*Packaging and storage, Chromatographic purity*	30	6	2010
Leuprolide Acetate (new)	30	3	882
Levothyroxine Sodium—*Assay*	30	5	1630
Lidocaine Hydrochloride—*Assay*	31	2	415
Lidocaine Hydrochloride and Dextrose Injection—*Assay for dextrose*	30	5	1631
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	31	2	415
Liothyronine Sodium—*Assay*	30	5	1631
Lipid Injectable Emulsion (new)	31	2	416
Liotrix Tablets—*Assay*	30	5	1632
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution, Assay*	30	5	1633
Loratadine—*Labeling* (add), *USP Reference standards, Related compounds*	30	6	2011
Loratadine Oral Solution—*Antimicrobial effectiveness test* (delete), *Related compounds*	31	1	56
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	26	4	1050
Magnesium Chloride—*Identification, Insoluble matter*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	421
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Mangafodipir Trisodium—*Packaging and storage*	30	6	2014
Mannitol Injection—*Labeling*	28	1	73
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Mefloquine Hydrochloride (new)	31	2	422
Meloxicam (new)	31	1	57
Meperidine Hydrochloride—*Packaging and storage, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	62
Mephobarbital—*Assay*	30	5	1634
Mepivacaine Hydrochloride Injection—*Assay*	30	6	2017
Meprobamate Tablets—*Dissolution*	30	1	129
Mesalamine—*Related compounds*	31	2	424
Metformin Hydrochloride—*Packaging and storage*	31	1	62
Metformin Hydrochloride Extended Release Tablets (new)	31	3	772
Methenamine Tablets—*Dissolution*	30	1	130
Methenamine Hippurate Tablets—*Labeling* (add), *Dissolution*	31	1	63
Methocarbamol Tablets—*Dissolution*	30	1	130

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Methscopolamine Bromide (new)	31	2	425
Methscopolamine Bromide Tablets (new)	31	2	427
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Metolazone Tablets—*Assay*	29	6	1932
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate (new)	30	6	2017
Morphine Sulfate—*Packaging and storage*	30	5	1639
Morphine Sulfate Extended-Release Capsules—*Packaging and storage*	28	6	1822
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Nabumetone—*Related compounds*	31	1	63
Nabumetone Tablets—*Dissolution*	30	6	2019
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nalidixic Acid—*Assay*	30	1	132
Naltrexone Hydrochloride—*Limit of total solvents*	30	6	2019
Naproxen Delayed-Release Tablets—*Packaging and storage*	30	4	1264
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Nitrogen—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	3	708
Nitrogen 97 Percent —*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	3	708
Nitrous Oxide—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	3	707
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Nystatin—*Composition* (add)	30	1	141
Nystatin, Neomycin Sulfate, Thiostrepton, and Triamcinolone Acetonide Ointment—*Assay for nystatin*	30	6	2020
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole Delayed-Release Capsules—*Packaging and storage*	30	1	143
Ondansetron (new)	30	6	2021
Ondansetron Oral Solution—*Packaging and storage*	30	3	905
Ondansetron Orally Disintegrating Tablets (new)	30	6	2024
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxandrolone Tablets—*Labeling* (add), *Dissolution*	31	3	781
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new)	30	4	1276
Oxycodone Hydrochloride—*Limit of alcohol*	30	6	2027
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Paroxetine Tablets—*Identification A, C*	31	2	435
Paroxetine Hydrochloride—*USP Reference standards, Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine, Chromatographic purity*	31	1	69
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	72
Pentobarbital Sodium—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Perflutren Protein-Type A Microspheres for Injection—*Assay for protein [Footnote 9]*	30	5	1639

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Perflutren Protein-Type A Microspheres Injectable Suspension—*Assay for protein [Footnote 9]*	30	5	1640
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylephrine Bitartrate (new)	31	3	783
Phenylethyl Alcohol—*USP Reference standards*	30	4	1290
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Phenytoin Sodium—*Related compounds, Assay*	30	6	2030
Physostigmine Salicylate Injection—*USP Reference standards, Assay*	30	6	2031
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Bromide (new)	31	2	441
Potassium Chloride in Dextrose Injection—*Definition, Assay for dextrose*	30	5	1640
Potassium Chloride in Dextrose and Sodium Chloride Injection—*Assay for dextrose*	30	5	1641
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Prednisolone—*Chromatographic purity* (add), *Ordinary impurities* (delete)	30	5	1641
Prednisolone Acetate—*Identification C*	30	5	1642
Prilocaine (new)	30	5	1643
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propofol—*Packaging and storage, Labeling, USP Reference standards, Related compounds, Assay*	30	5	1645
Propoxycaine Hydrochloride—*Identification C*	30	6	2032
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Quinapril Tablets—*Packaging and storage*	29	4	1071
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards [USP Ranitidine Resolution Mixture RS], Chromatographic purity, Assay*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
Oral Rehydration Salts—*USP Reference standards* (add), *Assay for dextrose, Assay for citrate*	31	2	445
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Ringer's and Dextrose Injection—*Assay for dextrose*	30	5	1647
Ritonavir (new)	31	3	788
Ropivacaine Hydrochloride (new)	30	6	2039

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Saccharin Calcium (new)—*Harmonization*	36	2	607
Saccharin Sodium (new)—*Harmonization*	36	2	612
Sargramostim—*Definition*	30	6	2044
Scopolamine Hydrobromide—*Identification A*	31	1	73
Sevoflurane (new)	30	1	178
Simvastatin—*Packaging and storage, Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Human Fibroblast-Derived Temporary Skin Substitute (new)	30	4	1211
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bromide (new)	31	2	446
Sodium Chloride—*Identification, Loss on drying, Limit of potassium*	31	3	795
Sodium Chloride and Dextrose Tablets—*Assay for dextrose*	30	5	1647
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Sotalol Hydrochloride—*Related compounds*	30	6	2044
Soybean Oil—*Definition, Labeling* (add)	30	5	1648
Spironolactone Oral Suspension (new)	30	3	929
Spironolactone Tablets—*Assay*	31	1	74
Spironolactone and Hydrochlorothiazide Oral Suspension (new)	30	3	930
Stavudine—*Packaging and storage*	30	3	932
Succinylcholine Chloride—*Chromatographic purity*	31	1	74
Sufentanil Citrate Injection—*Identification A*	30	6	2045
Sulfamethazine Granulated—*Assay*	31	3	797
Sumatriptan Nasal Spray (new)	30	6	2045
Talc (new)—*Harmonization*	30	5	1859
Technetium 99Tc Fanolesomab Injection (new)	31	2	448
Terbutaline Sulfate—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	75
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Terbutaline Sulfate Tablets—*USP Reference standards, Dissolution*	31	1	76
Testosterone Enanthate—*Water*	30	5	1648
Tetracaine Hydrochloride—*Identification A*	31	2	451
Tetracaine Hydrochloride in Dextrose Injection—*Assay for dextrose*	30	5	1648
Thalidomide—*Chromatographic purity*	31	2	452
Theophylline in Dextrose Injection—*Assay for dextrose*	30	5	1649
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Thioguanine—*Definition, Nitrogen content, Limit of guanine* (add), *Assay*	30	6	2049
Thioridazine Hydrochloride—*Identification*	31	3	798
Tiagabine Hydrochloride—*Chromatographic purity*	30	5	1649
Tiamulin (new)	31	1	77
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Titanium Dioxide (NL to come)—*New Monograph [UV Attenuation]*	30	4	1304
Tizanidine Tablets (new)	31	2	456
Tizanidine Hydrochloride (new)	31	2	452
Tolcapone—*Definition, Absorptivity, Related compounds*	30	6	2051
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate*	31	2	465

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Triclosan—*USP Reference standards, Limit of monochlorophenols and 2,4-dichlorophenol, Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran*	30	6	2054
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Ursodiol Capsules—*Dissolution*	31	3	800
Valsartan (new)	29	6	1996
Valsartan and Hydrochlorothiazide Tablets (new)	29	6	2000
Valpoic Acid Injection (new)	31	3	801
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add), *Chromatographic purity*	30	6	2055
Vecuronium Bromide (new)	30	6	2057
Purified Water—*Definition*	31	2	467
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins, Oxidizable substances*	31	2	468
Water for Injection—*Definition, Bacterial endotoxins*	31	2	466
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Small Intestinal Submucosa Wound Matrix (new)	30	5	1652
Zinc Oxide—*Iron and other heavy metals*	31	1	80
Zinc Oxide Neutral (new)	31	1	80
Zinc Sulfate Oral Solution (new)	31	2	468
Zinc Sulfate Tablets (new)	31	1	82
Dietary Supplements Monographs			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Choline Chloride—*Limit of total amines*	31	1	84
Chondroitin Sulfate Sodium Tablets—*Labeling*	31	1	85
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Chondroitin Sulfate Sodium—*Labeling*	30	6	2068
Chromium Picolinate Tablets (new)	30	5	1664
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Ginger Capsules (new)	28	3	814
Powdered Ginkgo Extract (new)	27	2	2233
Ginkgo Capsules (new)	27	2	2238
Ginkgo Tablets (new)	27	2	2240
American Ginseng Capsules (new)	30	2	565
American Ginseng Tablets—*Dissolution [to come]*	30	2	567
Asian Ginseng Capsules (new)	30	2	571
Lycopene (new)	30	6	2073
Lycopene Preparation (new)	30	6	2075
Lysine Hydrochloride Tablets (new)	30	5	1665
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474

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Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Psyllium Husk—*Definition, Light extraneous matter, Heavy extraneous matter* (delete)	30	6	2077
Pygeum Extract—*Packaging and storage*	30	3	956
Selenomethionine—*USP Reference standards, Assay*	31	2	482
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Tomato Extract Containing Lycopene (new)	30	2	578
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian Capsules (new)	27	1	1825
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition*	31	2	504
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192
⟨11⟩ USP Reference Standards—	26	3	793
	26	4	1101
	26	5	1369
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	4	1224
	28	5	1468
	28	6	1913
	29	3	710
	29	4	1137
	29	5	1601
	29	6	2022
	30	1	211
	30	2	613
	30	3	998
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
⟨41⟩ Weights and Balances—*Introduction, Weights, Balances*	31	2	508
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Procedures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Introduction, Rabbit Blood Sugar Method—Quantitative, Diluent, Standard Stock Solution, Standard Solutions, Assay Stock Solution, Assay Solutions, Procedure, Blood Samples, Calculation, Appendix* (add)	30	5	1675

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⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨341⟩ Antimicrobial Agents—Contents—*General Gas Chromatographic Method, Polarographic Method*	30	5	1678
⟨345⟩Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨386⟩ Environmentally Sensitive Preparations (new)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	28	3	895
⟨611⟩ Alcohol Determination—*Method II–Gas-Liquid Chromatographic Method*	31	3	823
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Introduction, Thin-Layer Chromatography, Interpretation of Chromatograms, System Suitability, Glossary of Symbols, Chromatographic Reagents*	31	3	825
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨711⟩ *Dissolution Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain-coated Tablets* (delete)	30	1	234
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	30	6	2235
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨776⟩ Optical Microscopy (new)—*Harmonization*	30	6	2212
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨786⟩ Particle Size Distribution Estimation by Analytical Sieving (new)—*Harmonization*	30	6	2216
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨841⟩ Specific Gravity—*Introduction, Method I, Method II* (add)	31	2	515
⟨851⟩ Spectrophotometry and Light-Scattering—*Procedure*	30	5	1703
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
General Information Chapters			
⟨1065⟩ Ion Chromatography (new)	31	2	519
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1075⟩ Good Compounding Practices—*Introduction, Applicable Definitions, Responsibilities of the Compounder, Training, Procedures and Documentation, Drug Compounding Facilities, Drug Compounding Equipment, Component Selection Requirements, Packaging and Drug Product Containers, Compounding Controls, Labeling, Records and Reports, Compounding for a Prescriber's Office Use, Compounding Veterinarian Products, Compounding Pharmacy Generated Products* (delete)	31	1	101
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1079⟩ Good Storage and Shipping Practices (new)	30	6	2118
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	28	5	1650
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1101⟩ Medicine Dropper—*Introduction*	30	6	2137

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⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709
⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add), *Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1119⟩ Near-Infrared Spectrophotometry—*Instrumentation*	30	6	2137
⟨1120⟩ Raman Spectrophotometry (new)	30	6	2139
⟨1136⟩ Packaging—Unit-of-Use (new)	30	5	1722
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1174⟩ Powder Flow (new)—*Harmonization*	30	6	2226
⟨1177⟩ Good Packaging Practices (new)	30	6	2152
⟨1178⟩ Good Repackaging Practices (new)	30	6	2156
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1216⟩ Tablet Friability *(Harmonization)—Introduction and text*	30	5	1740
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	29	1	256
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1231⟩ Water for Pharmaceutical Purposes (new)	30	5	1744
⟨1232⟩ Instrumentation for Analysis of High Purity Pharmaceutical Waters (new)	30	5	1806
⟨1265⟩ Written Prescription Drug Information—Guidelines (new)	30	3	1040
⟨2023⟩ Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements—*Supplement Components, Microbiological Testing*	30	5	1818
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
Reagent Specifications			
Acetal	30	2	644
Acetanilide	31	2	572

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Acetylcholine Chloride	31	2	573
4-Amino-6-chloro-1,3-benzenedisulfonamide	31	2	573
Amyl Acetate	31	2	574
tert-Amyl Alcohol	31	2	574
Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form	31	3	858
L-Asparagine	31	2	574
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (add)	29	1	265
Benzaldehyde	31	2	574
Benzphetamine Hydrochloride	31	2	575
Benzyltrimethylammonium Chloride	31	2	575
Biphenyl	31	2	575
N-Bromosuccinimide	31	2	575
2,3-Butanedione	31	2	576
n-Butyl Chloride	31	2	576
Cadmium Acetate	31	2	576
Calcium Citrate	31	2	577
Calcium Lactate	31	2	577
Calf Thymus DNA	30	4	1389
Casein	31	2	578
Charcoal, Activated	31	2	578
Chlorobenzene	31	2	578
4-Chlorophenol (delete)	30	6	2168
Chromotrope 2R	30	4	1390
Citric Acid	30	3	1044
Citric Acid, Anhydrous	30	3	1044
Collagen	30	4	1390
Rat Tail Collagen	30	2	644
Collagenase	30	4	1390
Congo Red	31	2	578
Cyclohexanol	31	2	579
Deuterated Methanol (new)	29	6	2054
o-Dichlorobenzene	31	2	579
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl	31	3	858
Dicyclohexyl Phthalate (add)	26	2	504
Dicyclohexylamine	31	2	579
Diidofluorescein	31	2	579
DEAE-Agarose (add)	29	1	265
1,2-Dimethoxyethane	31	2	580
N,N-Dimethyldodecylamine-*N*-oxide (add)	27	4	2837
Dodecyltrimethylammonium Bromide (new)	31	3	859
Ethyl Cyanoacetate	31	2	580
Ethylene Glycol	31	2	580
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
Fast Green FCF	30	4	1391
Ferric Ammonium Citrate	31	2	581
Guaiacol	31	2	581
Heptakis (2,6-di-*O*-methyl)-β-cyclodextrin (new)	30	6	2169
n-Heptane, Chromatographic	31	2	581
Hexadimethrine Bromide (add)	29	1	265
Hexamethyldisilazane	31	2	581
Hexane, Solvent	31	2	582
2′-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5′-bi-1*H*-benzimidazole Trihydrochloride Pentahydrate	30	4	1391
Inositol	31	2	582
Isoferulic Acid (add)	27	4	2837
Isopropylamine	31	2	582
Lanthanum Oxide (add)	28	3	851
Maleic Acid	31	2	583

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Methyl Acetate	31	2	583
4-Methylpentan-2-ol	30	2	646
Methyl Red (add)	31	1	108
1-Naphthol	31	2	583
2-Naphthol	31	2	583
5-Nitro-1,10-phenanthroline	31	2	584
Nonylphenoxypoly(ethyleneoxy)ethanol	31	2	584
Para-aminobenzoic Acid	31	2	584
Paraformaldehyde	31	2	584
Piperazine (new)	30	5	1821
Propionic Anhydride	31	2	585
Pyrrole	31	2	585
Direct Red 80	30	4	1390
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Rose Bengal Sodium	31	2	585
Thrombin Human (new)	29	6	2055
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
Silver Oxide	31	2	585
Sodium Arsenite	31	2	586
Sodium Chromate	31	2	586
Sodium Glycocholate	31	2	587
Sodium 1-Hexanesulfonate Monohydrate (new)	31	2	587
Tetramethylammonium Hydroxide	31	2	587
Thioglycolic Acid	31	2	587
Thymol	31	2	588
n-Tricosane	31	2	588
Triethylamine	31	2	588
2,4,6-Trimethylpyridine	31	2	588
Vinyl Acetate	30	6	2169
1-Vinyl-2-pyrrolidone	31	1	108
Zinc Sulfate Heptahydrate (add)	26	2	504
Test Solutions			
Phenol TS (new)	31	3	859
Sodium Citrate TS, Alkaline (new)	31	3	859
Volumetric Solutions			
Ceric Sulfate, Tenth-Normal (0.1 N)	31	1	109
Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol	31	1	112
Reference Tables			
Container Specifications for Capsules and Tablets	31	3	859
Excipients, USP and NF Excipients, Listed by Category	29	4	1088
	29	6	2008
	30	4	1317
	30	5	1659
	30	6	2062
	31	3	805
Description and Solubility	25	4	8589
	25	6	9254
	26	4	1135
	27	1	1908
	28	2	554
	28	4	1236
	28	5	1542
	28	6	1953
	29	1	266
	29	4	1262

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	30	3	1050
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	30	5	1822
	30	6	2183
	31	1	122
	31	2	591
	31	3	861
NF Monographs			
Acesulfame Potassium—*Packaging and storage* (add)	31	1	87
Acetyltributyl Citrate—*Assay*	30	6	2078
Acetyltriethyl Citrate—*Assay*	30	6	2079
Adipic Acid—*Packaging and storage* (add), *USP Reference standards* (add)	31	1	87
Alfadex—*Packaging and storage*	30	1	202
Ammonio Methacrylate Copolymer—*Identification B*	30	5	1666
Ammonio Methacrylate Copolymer Dispersion—*Identification A, B*	31	2	483
Asparagine—*Packaging and storage* (add), *USP Reference standards, Identification, Chromatographic purity*	31	1	87
Purified Bentonite—*Assay for aluminum and magnesium content*	31	2	483
Butylparaben (new)—*Harmonization*	31	1	191
Calcium Silicate—*Definition, pH, Limit of fluoride, Assay of silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	30	2	595
Carbomer 934—*Labeling*	31	2	484
Carbomer 934 P—*Labeling* (add), *Limit of benzene*	31	2	484
Carbomer 940—*Labeling, Viscosity*	31	2	485
Carbomer 941—*Labeling*	31	2	485
Carbomer 1342—*Labeling*	31	2	485
Carbomer Copolymer—*Definition, Labeling, Limit of benzene* (add), *Organic volatile impurities* (add), *Content of carboxylic acid*	31	2	486
Carbomer Homopolymer (new)	31	2	488
Carbomer Interpolymer—*Labeling, Limit of benzene* (add), *Organic volatile impurities* (add)	31	2	493
Cetostearyl Alcohol—*Assay*	31	2	494
Cetyl Alcohol—*Assay*	31	2	494
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Croscarmellose Sodium *(Harmonization)—Residue on ignition*	30	4	1439
Crospovidone—*Monograph*	28	4	1257
Galactose—*Packaging and storage* (add)	31	1	88
Glyceryl Monostearate—*USP Reference standards* (delete), *Hydroxyl value, Saponification value, Assay for monoglycerides*	31	2	495
Purified Honey (new)	31	2	496
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Hypromellose Acetate Succinate (new)	30	6	2079
Isomalt (new)	31	1	88
Lauroyl Macrogoglycerides (new)	28	4	1212
Lauroyl Polyoxylglycerides (new)	31	1	92
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate—*Harmonization*	30	1	340
Methacrylic Acid Copolymer—*Limit of monomers*	31	1	93
Monoglyceride Citrate (new)	30	6	2088
Myristic Acid (new)	30	5	1666
Neotame (new)	31	2	497
Phenolsulfonphthalein—*Labeling* (add), *USP Reference standards* (add), *Bacterial endotoxins* (add)	31	1	94
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Organic volatile impurities*	31	1	95

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Polyisobutylene—*Definition, Labeling, Molecular weight* (delete), *Viscosity* (add)	30	6	2089
Polyoxyl 35 Castor Oil—*USP Reference standards* (add), *Identification A*	30	5	1668
Propylene Glycol Dilaurate (new)	31	2	500
Propylene Glycol Monolaurate (new)	31	2	501
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618
Sesame Oil—*Definition, Labeling* (not NL issue), *USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Sodium Caprylate—*Packaging and storage*	30	3	990
Sodium Starch Glycolate—*Harmonization*	30	4	1455
Sodium Tartrate—*Packaging and storage*	31	1	95
Sorbitol Sorbitan Solution (Anhydrized Liquid Sorbitol) (new)	30	5	1669
Corn Starch—*Packaging and storage* (add)	30	5	1862
Potato Starch—*Packaging and storage* (add)	30	5	1865
Rice Starch (new)—*Harmonization*	30	2	721
Tapioca Starch—*Iron*	30	5	1672
Wheat Starch—*Packaging and storage* (add)	30	5	1868
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Succinic Acid—*Packaging and storage*	31	1	95
Sucrose—*Harmonization*	31	3	902
Sunflower Oil (new)	31	1	95
Tagatose (new)	30	5	1672
Tributyl Citrate—*Assay*	30	6	2091
Triethyl Citrate—*Assay*	30	6	2091
Medium-Chain Triglycerides—*Definition*	31	1	98

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USP Monographs			
Acepromazine Maleate—*Labeling, Other requirements*	29	6	1832
Acyclovir—*Labeling, USP Reference standards, Other requirements*	30	5	1580
Adenosine—*Labeling, USP Reference standards, Other requirements*	29	6	1834
†Medical Air—*Assay*	28	4	1065
Albendazole Oral Suspension—*Labeling*	29	4	991
Albuterol Tablets—*Assay*	31	1	40
Alcohol—*Harmonization*	30	2	670
Dehydrated Alcohol—*Harmonization*	30	2	673
Alfentanil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Alprostadil—*Labeling, USP Reference standards, Other requirements*	29	5	1412
Alteplase—*Labeling, Other requirements*	29	6	1835
Amifostine—*Labeling, USP Reference standards, Other requirements, Assay*	30	6	1974
Aminocaproic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Aminopentamide Sulfate—*Labeling, USP Reference standards, Other requirements*	30	4	1163
Aminophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Amitriptyline Hydrochloride—*Labeling, Other requirements*	29	6	1844
Ammonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1415
Ammonium Molybdate—*Labeling, Other requirements*	29	5	1416
Amphotericin B Lotion—*Title*	30	2	444
Amphotericin B Topical Emulsion (entire submission)	30	2	445
Anileridine—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atenolol—*Labeling, USP Reference standards, Other requirements*	29	5	1416
Atracurium Besylate—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atropine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1847
Aurothioglucose—*Labeling, Other requirements*	29	6	1847
Azaperone—*Labeling, Other requirements*	29	6	1847
Benzoyl Peroxide Lotion—*Title*	30	2	456
Benzoyl Peroxide Topical Emulsion (entire submission)	30	2	456
Benztropine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1848
Benzyl Benzoate Lotion—*Title*	30	2	457
Benzyl Benzoate Topical Emulsion (entire submission)	30	2	457
Betamethasone Tablets—*Identification, Thin-layer chromatographic identification test*	30	1	62
Betamethasone Dipropionate Lotion—*Title*	30	2	458
Betamethasone Dipropionate Topical Emulsion (entire submission)	30	2	459
Betamethasone Valerate Lotion—*Title*	30	2	461
Betamethasone Valerate Topical Emulsion (entire submission)	30	2	461
Bethanechol Chloride—*Labeling, USP Reference standards, Other requirements*	30	5	1586
Biperiden—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Bretylium Tosylate—*Labeling, USP Reference standards, Other requirements*	29	5	1431

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Bumetanide—*Labeling, USP Reference standards, Other requirements*	29	5	1432
Bupivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	5	1589
Butorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Caffeine—*Labeling, USP Reference standards, Other requirements*	30	4	1168
Calcium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1436
Carboprost Tromethamine—*Labeling, USP Reference standards, Other requirements*	30	1	82
Carboxymethylcellulose Sodium—*Harmonization*	28	3	867
Chlordiazepoxide Hydrochloride—*USP Reference standards*	29	6	1859
Chloroprocaine Hydrochloride—*Labeling, Other requirements*	29	5	1438
Chloroquine—*Labeling, USP Reference standards, Other requirements*	29	6	1859
Chlorothiazide—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1860
Chromic Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Cimetidine—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Ciprofloxacin Hydrochloride—*Labeling, Other requirements*	29	6	1861
Clonidine Hydrochloride Injection (new)—*Preview*	26	2	351
Clotrimazole Lotion—*Title*	30	2	473
Clotrimazole Topical Emulsion (entire submission)	30	2	474
Codeine Phosphate—*Labeling, USP Reference standards, Other requirements*	30	5	1597
Cortisone Acetate—*Labeling, Other requirements*	29	5	1447
Cupric Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1864
Cupric Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1447
Deslanoside—*Labeling, Other requirements*	29	5	1448
Desmopressin Acetate (new)—*Preview*	24	2	5773
Desmopressin Injection (new)—*Preview*	24	2	5778
Desmopressin Nasal Spray Solution (new)—*Preview*	24	2	5779
Desoxycorticosterone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1456
Desoxycorticosterone Pivalate—*Labeling, USP Reference standards, Other requirements*	29	6	1865
Dexamethasone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Dextran 1—*Other requirements*	29	6	1866
Dextran 40—*Other requirements*	29	6	1866
Dextran 70—*Other requirements*	29	6	1868
Dextrose—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Diatrizoate Meglumine—*Labeling, USP Reference standards, Other requirements*	30	3	832
Diatrizoate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1868

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Diazepam—*Labeling, USP Reference standards, Other requirements*	30	1	96
Diazoxide—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Dibucaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Dicyclomine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Diethylstilbestrol—*Labeling, USP Reference standards, Other requirements*	29	5	1463
Diethylstilbestrol Diphosphate Tablets (entire submission)	30	4	1187
Dihydroergotamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1870
Dimenhydrinate—*Labeling, Other requirements*	29	5	1466
Dimercaprol—*Labeling, Other requirements*	29	5	1466
Diphenhydramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1466
Dipyridamole—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dobutamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dolasetron Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1468
Dopamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1469
Doxapram Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1874
Doxycycline Hyclate—*Content of ethanol*	30	3	836
Droperidol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1875
Dyphylline—*Labeling, USP Reference standards, Other requirements*	29	5	1473
Edetate Calcium Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edetate Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edrophonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1475
Emetine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1875
Ephedrine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	3	840
Epinephrine—*Labeling, USP Reference standards, Other requirements*	29	5	1476
Ergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1478
Ergotamine Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1884
Estradiol—*Labeling, USP Reference standards, Other requirements*	29	5	1478
Estrone—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Ethacrynic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Fenoldopam Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Fentanyl Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1885
Flunixin Meglumine—*Labeling, USP Reference standards, Other requirements*	29	6	1886

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Fluphenazine Enanthate—*Labeling, USP Reference standards, Other requirements*	29	6	1887
Fluphenazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1888
Flurandrenolide Lotion—*Title*	30	2	489
Flurandrenolide Topical Emulsion (entire submission)	30	2	489
Fosphenytoin Sodium—*Labeling, Other requirements*	29	6	1888
Fructose—*Labeling, USP Reference standards, Other requirements*	29	5	1496
Furosemide—*Labeling, USP Reference standards, Other requirements*	29	5	1497
Gabapentin (entire submission)	29	1	72
Gadodiamide—*Labeling, Other requirements*	29	6	1889
Gadoteridol—*Labeling, USP Reference standards*	29	6	1890
Gallamine Triethiodide—*Labeling, USP Reference standards, Other requirements*	29	5	1503
Ganciclovir—*Labeling, USP Reference standards, Other requirements*	29	6	1890
Glucagon—*Labeling, USP Reference standards, Other requirements*	30	5	1625
Glycerin—*Labeling, Other requirements*	29	6	1895
Glycopyrrolate—*Labeling, USP Reference standards, Other requirements*	29	5	1503
Gold Sodium Thiomalate—*Labeling, Other requirements*	29	6	1895
Chorionic Gonadotropin—*Labeling*	29	6	1896
Haloperidol—*Labeling, USP Reference standards, Other requirements*	29	6	1897
†Helium—*Identification, Assay*	28	4	1121
Histamine Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1504
Hydralazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1505
Hydrocortisone—*Labeling, USP Reference standards, Other requirements*	29	5	1506
Hydrocortisone Lotion—*Title*	30	2	505
Hydrocortisone Topical Emulsion (entire submission)	30	2	506
Hydrocortisone Acetate Lotion—*Title*	30	2	504
Hydrocortisone Acetate Ointment—*Assay*	30	2	504
Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	504
Hydromorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	4	1254
Hydroxyprogesterone Caproate—*Labeling, Other requirements*	29	5	1506
Hydroxyzine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1902
Hyoscyamine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Imipramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1904
Inamrinone—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Indigotindisulfonate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1905
†Indinavir Sulfate Capsules (entire submission)	30	2	508
Insulin—*Labeling, Other requirements, Limit of high molecular weight proteins*	30	5	1629
Insulin Human—*Labeling, Other requirements*	29	6	1906

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Iodipamide—*Labeling, USP Reference standards, Other requirements*	29	6	1907
Iodixanol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1908
Iohexol—*Labeling, USP Reference standards, Other requirements*	29	6	1908
Iopamidol—*Labeling, USP Reference standards, Other requirements*	29	6	1909
Iophendylate—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Iothalamic Acid—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Ioversol—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Ioxaglic Acid—*Labeling, Other requirements*	29	6	1911
Ioxilan—*Labeling, Other requirements*	29	6	1911
Isoniazid—*Labeling, USP Reference standards, Other requirements*	29	6	1912
Isoproterenol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1509
Ketamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1913
Ketorolac Tromethamine—*Labeling, USP Reference standards, Other requirements*	29	6	1915
Labetalol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Leuprolide Acetate Injection (new)—*Preview*	25	5	8722
Levorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Levothyroxine Sodium Tablets—*Dissolution, Test 3*	29	3	634
Lidocaine Hydrochloride—*Assay*	30	4	1256
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	30	4	1257
Lindane Lotion—*Title*	30	2	512
Lindane Topical Emulsion (entire submission)	30	2	512
Lorazepam—*Labeling, USP Reference standards, Other requirements*	29	6	1918
Magnesium Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1921
Malathion Lotion—*Title*	30	2	513
Malathion Topical Emulsion (entire submission)	30	2	513
Mangafodipir Trisodium—*Labeling, Other requirements*	30	6	2014
Manganese Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1526
Manganese Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1922
Mannitol (entire submission)	27	5	3017
Mannitol Injection (entire submission)	27	5	3020
Mebrofenin—*Labeling, USP Reference standards, Other requirements*	29	6	1923
Medroxyprogesterone Acetate—*Labeling, Other requirements*	29	5	1526
Menadiol Sodium Diphosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1531
Menadione—*Labeling, USP Reference standards, Other requirements*	29	5	1531
Menotropins—*Labeling, Other requirements*	29	6	1923
Meperidine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1924

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Mesoridazine Besylate—*Labeling, USP Reference standards, Other requirements*	30	4	1262
Metaraminol Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1533
Methadone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1929
Methocarbamol—*Labeling, USP Reference standards, Other requirements*	29	6	1930
Methohexital—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methotrimeprazine—*Labeling, USP Reference standards, Other requirements*	29	6	1931
Methylbenzethonium Chloride Lotion—*Title*	30	2	515
Methylbenzethonium Chloride Topical Emulsion (entire submission)	30	2	515
Methylbenzethonium Chloride Topical Powder—*Assay*	30	2	516
Methyldopate Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylene Blue—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1535
†Methylphenidate Hydrochloride (new)—*Preview*	30	2	731
Methylprednisolone Acetate—*Labeling, Other requirements*	29	5	1535
Metoclopramide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1536
Metoprolol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1536
Metronidazole—*Labeling, USP Reference standards, Other requirements*	29	6	1933
Miconazole—*Labeling, USP Reference standards, Other requirements*	29	6	1934
Morphine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	5	1639
Nalorphine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1935
Naloxone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1936
Nandrolone Decanoate—*Labeling, Other requirements*	29	5	1539
Neomycin Sulfate and Flurandrenolide Lotion—*Title*	30	2	516
Neomycin Sulfate and Flurandrenolide Topical Emulsion (entire submission)	30	2	516
Neomycin Sulfate and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Lotion—*Title*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	519
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519

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* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519
Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neostigmine Methylsulfate—*Labeling, Other requirements*	29	6	1936
Diluted Nitroglycerin—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Norepinephrine Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Nystatin Lotion—*Title*	30	2	522
Nystatin Topical Emulsion (entire submission)	30	2	522
Ofloxacin—*Labeling, USP Reference standards, Other requirements*	30	4	1274
Ondansetron Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1941
Orphenadrine Citrate—*Labeling, USP Reference standards, Other requirements*	30	2	523
Oxandrolone—*Definition, Identification B, Ordinary impurities, Related compounds, Assay*	30	1	148
†Oxygen—*Identification, Assay*	28	4	1171
†Oxygen 93 Percent—*Identification, Assay*	28	4	1171
Oxymorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1946
Oxytocin—*Labeling, USP Reference standards, Other requirements*	29	6	1946
Paclitaxel—*USP Reference standards, Related compounds (C)*	30	4	1279
Padimate O Lotion—*Title*	30	2	527
Padimate O Topical Emulsion (entire submission)	30	2	527
Papaverine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1551
Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension—*Assay for hydrocortisone acetate*	30	2	528
Pentobarbital—*Labeling, USP Reference standards, Other requirements*	30	1	154
Pentobarbital Sodium—*Labeling, USP Reference standards, Other requirements*	30	1	157
Perphenazine—*Labeling, USP Reference standards, Other requirements*	29	6	1963
Phenobarbital—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phentolamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1562
Phenylbutazone Injection—*USP Reference standards*	29	6	1964
Phenylephrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phenytoin Sodium—*Labeling, USP Reference standards, Other requirements*	30	6	2030
Physostigmine Salicylate—*Labeling, USP Reference standards, Other requirements*	29	6	1967
Potassium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1562
Dibasic Potassium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1563
Prednisolone Acetate—*Labeling, Other requirements*	30	5	1642
Prilocaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1564

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[*PF* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
	Vol.	*No.*	*Page(s)*
Procainamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1565
Prochlorperazine Edisylate—*Labeling, USP Reference standards, Other requirements*	29	5	1565
Progesterone—*Labeling, Other requirements*	29	5	1566
Promazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1566
Promethazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1567
Propoxycaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	6	2032
Propranolol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Propyliodone—*Labeling, Other requirements*	29	6	1976
Pyridostigmine Bromide—*Labeling, USP Reference standards, Other requirements*	29	6	1977
Quinidine Gluconate—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Ranitidine Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	28	2	360
Reserpine—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Ritodrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Selenious Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1571
Sodium Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1576
Sodium Bicarbonate—*Labeling, USP Reference standards, Other requirements*	29	5	1577
Sodium Nitrite—*Labeling, USP Reference standards, Other requirements*	29	5	1577
Dibasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1578
Monobasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
Sodium Sulfate—*Labeling, Other requirements*	29	5	1579
Sodium Thiosulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
Sufentanil Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1988
Sulfadiazine Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1988
Sulfamethoxazole—*Labeling, Other requirements*	29	6	1989
Terbutaline Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Terbutaline Sulfate Inhalation Aerosol (entire submission)	26	3	753
Terbutaline Sulfate Injection—*USP Reference standards, Identification, Assay*	26	3	756
Testosterone—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Theophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiopental Sodium—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiothixene Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
Tolazoline Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1588

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[*PF* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Triamcinolone Acetonide—*Labeling, USP Reference standards, Other requirements*	30	3	945
Triamcinolone Acetonide Lotion—*Title*	30	2	538
Triamcinolone Acetonide Topical Emulsion (entire submission)	30	2	538
Trifluoperazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
Triflupromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1994
Trimethobenzamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1589
Trimethoprim—*Labeling, Other requirements*	29	6	1995
Trimethoprim Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1995
Tubocurarine Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1996
Urofollitropin (new) (entire submission)	28	6	1875
Urofollitropin for Injection (new) (entire submission)	28	6	1881
Valproic Acid Injection (new)—*Preview*	26	4	939
Vasopressin—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Verapamil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1598
Xylazine—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Xylazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
Yohimbine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
Zidovudine—*Labeling, USP Reference standards, Other requirements*	29	6	2006
Dietary Supplements Monographs			
†*Echinacea angustifolia—Microbial limits*	30	2	552
†Eleuthero—Microbial limits	26	6	1596
Fish Oil Rich in Omega-3 Acids (new) (entire submission)	29	4	1272
Fish Oil Rich in Omega-3 Acids Capsules (new) (entire submission)	29	4	1278
†Ginger Capsules—*Microbial limits*	28	3	814
†Asian Ginseng—*Microbial limits*	30	2	569
†Goldenseal—*Microbial limits*	30	3	952
†Licorice—*Microbial limits*	26	5	1363
†Powdered Licorice Extract—*Microbial limits*	30	2	574
Shark Liver Oil (new)—*Preview*	26	6	1643
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS	30	6	2092
USP Fluoxetine Related Compound B Solution RS	30	4	1338
†*USP Methylphenidate Related Compound B RS*	30	2	613
†*USP Methylphenidate Related Compound C RS*	30	2	613
†*USP Methylphenidate Related Compound D RS*	30	2	613
†*USP Methylphenidate Related Compound E RS*	30	2	613
†*USP Methylphenidate Related Compound F RS*	30	2	613
†*USP Methylphenidate Related Compound G RS*	30	2	613
†*USP Methylphenidate Related Compound H RS*	30	2	613
USP Paclitaxel Related Compound C RS	30	4	1338
USP Phenylephrine Bitartrate RS	30	3	998
USP Tazobactam Sodium RS	29	3	711
⟨601⟩ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers—*Harmonization*	28	2	584

In-Process Revision

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* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨621⟩ Chromatography—*Chromatographic Reagents, Phases* (Docosahexaenoic Acid)	29	6	2023
⟨643⟩ Total Organic Carbon (entire submission)	30	5	1700
⟨701⟩ Disintegration—*Harmonization*	28	5	1575
⟨711⟩ Dissolution—*Harmonization*	28	6	1981
⟨776⟩ Optical Microscopy—*Harmonization*	28	2	606
⟨786⟩ Particle Size Distribution by Analytical Sieving—*Harmonization*	28	5	1581
⟨811⟩ Powder Fineness (entire submission)	28	2	611
⟨943⟩ X-Ray Diffraction—Solids (new) (entire submission)	28	3	905
USP General Information Chapters			
⟨1174⟩ Powder Flow (new)—*Harmonization*	28	2	618
⟨1198⟩ Standardized Imprint Codes for Solid Oral Dosage Forms (new)—*Preview*	28	1	152
⟨1225⟩ Validation of Compendial Methods—*Validation—Ruggedness*	30	4	1382
Dietary Supplements Chapters			
†⟨2091⟩ Weight Variation of Nutritional Supplements (entire submission)	28	5	1548
Reagents, Indicators, and Solutions			
†Air–Nitrous Oxide Certified Standard (added)	28	4	1233
4-Chlorophenol (added)	30	3	1045
Dioleoylglycerol (added)—*Preview*	26	6	1622
Monooleoylglycerol (added)—*Preview*	26	6	1622
Pentadecanoic Acid Methyl Ester (added)—*Preview*	26	6	1622
1,1,4,4-Tetraphenyl-1,3-butadiene (added)	26	6	1623
Trioleoylglycerol (added)—*Preview*	26	6	1623
Reference Tables			
Container Specifications			
Diethylstilbestrol Diphosphate Tablets	30	4	1404
Description and Relative Solubility			
†Polydecene (added)	30	4	1405
Excipients			
†Polydecene	30	4	1317
NF Monographs			
Adipic Acid—*Packaging and storage*	30	4	1322
†Cellaburate—*Packaging and storage*	30	3	967
Microcrystalline Cellulose *(Harmonization)—Packaging and storage*	30	4	1435
Powdered Cellulose *(Harmonization)—Packaging and storage*	30	4	1438
Docosahexaenoic Acid (new)—*Preview*	26	6	1648
Docosahexaenoic Acid Capsules (new)—*Preview*	26	6	1651
Docosahexaenoic Acid Oil (new)—*Preview*	26	6	1652
Ethylparaben *(Harmonization)—Packaging and storage*	30	4	1444
†Maltol—*Packaging and storage*	30	3	984
Medium-Chain Triglycerides—*Packaging and storage*	30	3	998
Methylparaben *(Harmonization)—Packaging and storage*	30	4	1446
†Nitrogen—*Assay*	28	4	1219
†Nitrogen 97 Percent—*Assay*	28	4	1220
Phenoxyethanol—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94
†Polydecene (entire submission)	30	4	1331
†Polyethylene Glycol (entire submission)—*Preview*	29	4	1313
†Propylparaben *(Harmonization)—Packaging and storage*	30	4	1448

†New cancellations in *PF* 31(4).

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

Saccharin Sodium, *USP 28* page 1745 and page 612 of *PF* 31(2) [Mar.–Apr. 2005]. 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.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification B	+	+	+
Identification C	–	+	+
Acidity or alkalinity	+	+	+
Water	+	+	+
Readily carbonizable substances	+	+	+
Limit of benzoate and salicylate	–	+	+
Assay	+	+	+

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Packaging and storage, Heavy metals, Labeling, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification A (IR).

Specific local attributes: USP: Organic volatile impurities; JP: Description.

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

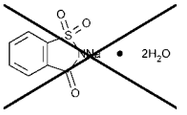
Differences between the **ADOPTION STAGE 6** document and the current *NF* monograph include the following:

(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 at room temperature are added.
(3) *Labeling*—No change.
(4) *USP Reference standards*—A reference for Saccharin Sodium is added for use in the *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 two tests (*B* and *C*). Because the preparation of potassium pyroantimonate TS has changed, the preparation of the potassium pyroantimonate solution for this test is added to comply with the harmonization draft.
(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. The *Test solution* is corrected to that of the EP. Editorial changes are made.
(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—42529-1

Change to read:

~~Saccharin Sodium~~



~~$C_7H_4NNaO_3S \cdot 2H_2O$ 241.20~~
~~1,2-Benzisothiazol-3(2*H*)-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*].~~

~~» Saccharin Sodium contains not less than 98.0 percent and not more than 101.0 percent of $C_7H_4NNaO_3S$, calculated on the anhydrous basis.~~

~~**Packaging and storage**—Preserve in well-closed containers.~~

~~**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 o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*~~

~~**Identification—**~~

~~**A:** The residue obtained by igniting it responds to the tests for *Sodium* ⟨191⟩.~~

~~**B:** To 10 mL of a solution (1 in 10) add 1 mL of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate with cold water until the last washing is free from chloride, and dry at 105° for 2 hours: it melts between 226° and 230°, the procedure for *Class I* being used (see *Melting Range or Temperature* ⟨741⟩).~~

~~**Alkalinity**—A solution (1 in 10) is neutral or alkaline to litmus, but no red color is produced with phenolphthalein TS.~~

~~**Toluenesulfonamides—**~~

~~*Internal standard solution*, *Standard stock solution*, and *Standard preparations*—Prepare as directed for *Internal standard solution*, *Standard stock solution*, and *Standard preparations* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph).~~

~~*Test preparation*—Prepare as directed under *Column Partition Chromatography* (see *Chromatography* ⟨621⟩), employing a chromatographic tube fitted with a porous glass disk in its base, a plastic stopcock on the delivery tube, and a reservoir on the top. Add a mixture consisting of 10 g of *Solid Support* and a solution of 2.0 g, accurately weighed, of Saccharin Sodium in 8.0 mL of sodium carbonate solution (1 in 20), and proceed as directed under *Test preparation* in the test for *Toluenesulfonamides* under *Saccharin* (see *NF* monograph), beginning with "Pack the contents."~~

~~*Chromatographic system* and *Procedure*—Proceed as directed for *Chromatographic system* and *Procedure* in the test for *Toluenesulfonamide* under *Saccharin* (see *NF* monograph).~~

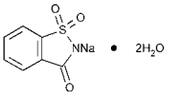
~~**Heavy metals,** *Method I* ⟨231⟩—Dissolve 4 g in 46 mL of water, add 4 mL of 1 N hydrochloric acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, and then filter through a dry filter, discarding the first 10 mL of the filtrate: the limit, determined on 25 mL of the subsequent filtrate, is 0.001%.~~

~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.~~

~~**Other requirements**—It responds to *Identification* tests *A* and *B*, and meets the requirements of the tests for *Water*, *Benzoate and salicylate*, *Selenium*, and *Readily carbonizable substances* under *Saccharin Calcium*.~~

~~**Assay**—Proceed with Saccharin Sodium as directed in the *Assay* under *Saccharin Calcium*. Each mL of 0.1 N sodium hydroxide is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.~~

■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*].

» 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.~~ 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 *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—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with ~~water~~ the same solution 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 of the 200 g per L solution of sodium acetate, or its 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—Use the *Test solution* from the test for *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 of 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~~ *Potassium pyroantimonate solution,* 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.

Potassium pyroantimonate solution—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly, and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution (8.5 in 100). Allow to stand for 24 hours, filter, and dilute with water to 150 mL.

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 10 N sodium hydroxide.~~ Dissolve 10.0 g of the substance to be examined in about 45 mL of water. If necessary, adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 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~~ gas chromatograph is equipped with a flame-ionization detector and contains a 0.53-mm × 10-m fused silica column, coated with G3 phase (film thickness 2 µm). The injector port, column, and detector temperatures are maintained at 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 $C_7H_4NNaO_3S$. ■2S (*USP29*)

MONOGRAPHS (NF)

BRIEFING

Silicon Dioxide, *NF 23* page 3073 and page 7187 of *PF* 24(6) [Nov.–Dec. 1998]. The Japanese Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of the compendial standards for the *Silicon Dioxide* 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 Revised **OFFICIAL INQUIRY STAGE 4** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 4 draft prepared by the Japanese Pharmacopoeia.

Differences between the Revised **OFFICIAL INQUIRY STAGE 4** document and the current *NF* monograph include the following:

(1) In the opening paragraph (the Definition)—The Definition is modified to include the term, "separating," to allow for the two processes of manufacturing, gel and precipitate. An upper limit for *Assay* is added. The current EP lower limit of 98.0% is adopted.
(2) *Packaging and storage*—No change. The *USP* text is retained as a nonharmonized attribute.
(3) *Labeling*—The requirement to label the different types of silica are omitted, because the Definition is changed. A requirement to label with the bulk density is added.
(4) *Identification*—Two additional identification procedures are added to strengthen the monograph.
(5) *pH*—The limit is unchanged, but the slurry concentration is slightly less.
(6) *Loss on drying*—The drying time and temperature are changed to 2 hours and 105°, respectively, and the limit is increased to 7.0%, as related to the time and temperature change.
(7) *Loss on ignition*—The ignition time is increased from 1 hour to 2 hours.
(8) *Heavy metals*—The *USP* test is retained as a nonharmonized attribute.
(9) *Chloride*—The test is omitted, because it is not necessary.
(10) *Hydrochloric acid soluble substances*—This test is added to indirectly control levels of aluminum and calcium.
(11) *Sulfate*—The *JP* test is adopted and the limit is increased to 1.0%.
(12) *Organic volatile impurities*—This test is retained as a specific local attribute for *USP.*
(13) *Arsenic*—This test is retained as a nonharmonized attribute.
(14) *Iron*—This test is added to limit iron impurities.

(15) *Bulk density*—This physical test procedure is added with no limits.
(16) *Assay*—This test is revised, but the scientific principles are the same as the current test.

Readers are requested to review the proposal carefully and to send comments to USP; the deadline for receipt is **30 September 2005.**

(EMC: J. Lane) RTS—41934-1

Add the following:

Silicon Dioxide

SiO_2xH_2O

Anhydrous 60.08

» Silicon Dioxide is prepared by separating from a sodium silicate solution with the addition of mineral acids, purifying, drying, and pulverizing. Silicon Dioxide, when ignited, contains not less than 98.0 percent and not more than 100.5 percent of SiO_2.

Packaging and storage—Preserve in tight containers, protected from moisture.

Labeling—Label it to state the bulk density.

Identification—

A: Place 5 mg of Silicon Dioxide in a platinum crucible, and mix with 0.2 g of anhydrous potassium carbonate. Ignite the mixture in a burner flame for 10 minutes, until the crucible's bottom reddens. After cooling, dissolve the melt in 2 mL of water, warming if necessary. Add 2 mL of *Ammonium molybdate–nitric acid solution,* prepared as directed below, slowly to the solution: the solution develops a deep yellow color.

Ammonium molybdate–nitric acid solution—Dissolve 8 g of ammonium molybdate in diluted nitric acid (1 in 5) to make 100 mL. Prepare freshly before use.

B: Dissolve 0.1 g of Silicon Dioxide in 20 mL of sodium hydroxide TS by boiling, and add 12 mL of ammonium chloride TS: a white gelatinous precipitate is produced. The precipitate does not dissolve in dilute hydrochloric acid.

C: Disperse a small amount of Silicon Dioxide over water in a small beaker: it becomes wet and sinks.

pH ⟨791⟩**:** between 4.0 and 8.0, in a slurry prepared by combining about 1.0 g of Silicon Dioxide and 25 mL of carbon dioxide-free water and shaking.

Loss on drying ⟨731⟩—Dry about 1 g at 105° for 2 hours: it loses not more than 7.0% of its weight.

Loss on ignition ⟨733⟩—Ignite about 1 g of it, previously dried and accurately weighed, at 1000° for 2 hours: it loses not more than 8.5% of its weight.

Hydrochloric acid soluble substances—To about 2.5 g of Silicon Dioxide add 50 mL of dilute hydrochloric acid, and mix. Heat on a water bath for 30 minutes, stirring from time to time, and maintaining the original volume by adding dilute hydrochloric acid. Evaporate to dryness. Add to the residue a mixture of 8 mL of dilute hydrochloric acid and 24 mL of water. Heat to boiling and filter under reduced pressure through a sintered-glass filter. Wash the residue on the filter with a hot mixture of 3 mL of dilute hydrochloric acid and 9 mL of water. Wash it again with small quantities of water, combine the filtrate and washings, and dilute with water to 50 mL. In a platinum dish, evaporate 10.0 mL of the solution to dryness, and dry to a constant mass at 105°. The mass of the residue is not more than 10 mg (2.0%).

Sulfate—

Test solution—To about 1.2 g of Silicon Dioxide add 60 mL of water, shake, add 2 mL of hydrochloric acid, and boil for 10 minutes. After cooling, add water to make 100 mL, and filter. To 10 mL of the filtrate add water to make 100 mL. To 20 mL of this solution add 1 mL of dilute hydrochloric acid, and dilute with water to 50 mL.

Standard solution—To 0.50 mL of 0.01 N sulfuric acid VS, add 1 mL of dilute hydrochloric acid, and dilute with water to 50 mL.

Procedure—[NOTE—If the *Test solution* is not clear, filter both the *Test solution* and the *Standard solution.*] Add 2 mL of barium chloride TS to the *Test solution* and to the *Standard solution*, mix well, and allow to stand for 10 minutes. Compare the turbidity produced in both solutions against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩) by viewing downward or transversely: the turbidity of the *Test solution* is not greater than that of the *Standard solution* (not more than 1.0%).

Iron—

Test solution—To 50 mg of Silicon Dioxide add 10 mL of dilute hydrochloric acid, and heat for 10 minutes in a water bath while shaking. After cooling, add 0.5 g of tartaric acid, dissolve the tartaric acid with shaking, and add 1 drop of phenolphthalein TS. Add ammonia TS dropwise until the solution develops a pale red color. Add 20 mL of a pH 4.5 buffer solution prepared by dissolving 75.4 mL of glacial acetic acid and 111 g of sodium acetate in 1000 mL of water.

Standard solution—Add 10 mL of dilute hydrochloric acid to 1.5 mL of *Standard Iron Solution* (see *Iron* ⟨241⟩), and proceed as directed for the *Test solution* beginning with "add 0.5 g of tartaric acid."

Procedure—Dissolve 0.2 g of ascorbic acid in the *Test solution* and the *Standard solution*, and allow to stand for 30 minutes. Add 1 mL of a solution of 2,2′-bipyridine in alcohol (1 in 200), add water to make 50 mL, and allow to stand for 30 minutes. Add 2 mL of picric acid solution (3 in 1000) and 20 mL of ethylene chloride, and shake well. Collect the ethylene chloride layers, and filter through pledgets of absorbent cotton in funnels containing about 5 g of anhydrous sodium sulfate. Compare the colors of the solution from the *Test solution* and the *Standard solution*. The solution from the *Test solution* has no more color than that from the *Standard solution* (0.030%).

Arsenic, *Method I* ⟨211⟩**—**Prepare the *Test Preparation* as follows. Transfer 4.0 g to a platinum dish, add 5 mL of nitric acid and 35 mL of hydrofluoric acid, and evaporate on a steam bath. Cool, add 5 mL of perchloric acid, 10 mL of hydrofluoric acid, and 10 mL of sulfuric acid, and evaporate on a hot plate to the production of heavy fumes. Cool, cautiously transfer to a 100-mL beaker with the aid of a few mL of hydrochloric acid, and evaporate to dryness. Cool, add 5 mL of hydrochloric acid, dilute with water to about 40 mL, and heat to dissolve any residue. Cool, transfer to a 100-mL volumetric flask, dilute with water to volume, and mix. A 25.0-mL portion of this solution meets the requirements of the test. The limit is 3 ppm.

Heavy metals, *Method I* ⟨231⟩**—**Transfer 16.7 mL of the solution prepared for the test for *Arsenic* into a 100-mL beaker, and neutralize with ammonium hydroxide to litmus paper. Adjust with 6 N acetic acid to a pH of between 3 and 4.

Filter, using medium-speed filter paper, wash with water until the filtrate and washings measure 40 mL, and mix. The limit is 0.003%.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Bulk density—Place a No. 70 sieve (212 µm) at a position of about 20 cm above a tared brass or stainless steel cup, which has the capacity of 25.0 ±0.05 cm^3 and an inside diameter of 30.0 ±2.0 mm, and slowly pour Silicon Dioxide through the sieve, at a rate suitable to prevent clogging until the cup overflows. Level the excess powder with the aid of a slide glass, weigh the filled cup, and weigh accurately the content of the cup, and then calculate the bulk density by the following expression: the bulk density is within the labeled specification.

$$\text{Bulk density } (g/cm^3) = A/25$$

where A is the measured mass of the content of the cup (g).

Assay—Accurately weigh and transfer about 1 g *(m)* of Silicon Dioxide, that has been previously ignited at 1000° for 2 hours after drying at 105° for 2 hours, to a tared platinum dish (previously ignited at 1000° for 30 minutes), weigh the dish, and designate the mass as a (g). Moisten the sample with 4 drops of alcohol and 2 drops of sulfuric acid, add 15 mL of hydrofluoric acid, and evaporate to dryness on a water bath with a well-ventilated hood. After cooling, add about 5 mL of hydrofluoric acid and evaporate to dryness. Heat the residue at 550° for 1 hour, gradually increasing the temperature, and ignite at 1000° for 30 minutes. Cool in a desiccator, weigh the dish, and designate the mass as b (g). Calculate the percentage of SiO_2 using the following formula:

$$[(a - b)/m] \times 100$$

BRIEFING

Colloidal Silicon Dioxide, *NF 23* page 3074 and page 7187 of *PF* 24(6) [Nov.–Dec. 1998]. The Japanese Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of the compendial standards for the *Colloidal Silicon Dioxide* 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 Revised **OFFICIAL INQUIRY STAGE 4** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 4 draft prepared by the Japanese Pharmacopoeia.

Differences between the Revised **OFFICIAL INQUIRY STAGE 4** document and the current *NF* monograph include the following:

(1) In the opening paragraph (the Definition)—The Definition is modified to include an example of silicon tetrachloride and the temperature at which the hydrolysis takes place.
(2) *Packaging and storage*—No change. The *USP* text is retained as a nonharmonized attribute.
(3) *Labeling*—Requirement to label with the bulk density is added.
(4) *Identification*—Two additional identification procedures are added to strengthen the monograph.
(5) *pH*—No change.
(6) *Loss on drying*—The limit is increased to 5.0%.
(7) *Loss on ignition*—The ignition time is specified as 2 hours, and the limit is increased to 6.0%.
(8) *Heavy metals*—The *USP* test is retained as a nonharmonized attribute.
(9) *Chloride*—The test is added, because chloride containing compounds may be used in the manufacture of this article.
(10) *Organic volatile impurities*—This test is retained as a specific local attribute for *USP.*
(11) *Arsenic*—This test is retained as a nonharmonized attribute.
(12) *Bulk density*—This physical test procedure is added with no limits.
(13) *Assay*—This test is revised, but the scientific principles are the same as the current test.

Readers are requested to review the proposal carefully and to send comments to USP; the deadline for receipt is **30 September 2005.**

(EMC: J. Lane) RTS—41934-2

Add the following:

Colloidal Silicon Dioxide

SiO_2 60.08

Silica.

Silica [*7631-86-9*].

» Colloidal Silicon Dioxide is prepared by hydrolyzing a silicon compound, such as silicon tetrachloride, at a temperature of at least 1000° by vapor phase hydrolysis process. When ignited at 1000°, it contains not less than 99.0 percent and not more than 100.5 percent of SiO_2.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate the bulk density.

Identification—

A: Place 5 mg of Colloidal Silicon Dioxide in a platinum crucible, and mix with 0.2 g of anhydrous potassium carbonate. Ignite the mixture in a burner flame for 10 minutes until the crucible's bottom reddens. After cooling, dissolve the melt in 2 mL of water, warming if necessary. Add 2 mL of *Ammonium molybdate–nitric acid solution,* prepared as directed below, slowly to the solution: the solution develops a deep yellow color.

Ammonium molybdate–nitric acid solution—Dissolve 8 g of ammonium molybdate in diluted nitric acid (1 in 5) to make 100 mL. Prepare freshly before use.

B: Dissolve 0.1 g of Colloidal Silicon Dioxide in 20 mL of sodium hydroxide TS by boiling, and add 12 mL of ammonium chloride TS: a white gelatinous precipitate is produced. The precipitate does not dissolve in dilute hydrochloric acid.

C: Disperse a small amount of Colloidal Silicon Dioxide over water in a small beaker: it becomes wet and sinks.

pH ⟨791⟩: between 3.5 and 5.5, in a slurry prepared by combining about 1.0 g of Colloidal Silicon Dioxide and 25 mL of carbon dioxide-free water and shaking.

Loss on drying ⟨731⟩—Dry about 1 g at 105° for 2 hours: it loses not more than 5.0% of its weight.

Loss on ignition ⟨733⟩—Ignite about 1 g of it at 1000° for 2 hours: it loses not more than 6.0% of its weight.

Arsenic, *Method I* ⟨211⟩—Prepare the *Test Preparation* as follows. Transfer 2.5 g to a flask, add 50 mL of 3 N hydrochloric acid, and reflux for 30 minutes using a water condenser. Cool, filter with the aid of suction, and transfer the filtrate to a 100-mL volumetric flask. Wash the filter and flask with several portions of hot water, and add the washings to the flask. Cool, dilute with water to volume, and mix: a 15.0-mL portion of this solution, to which 3 mL of hydrochloric acid has been added, meets the requirements of the test, the addition of the 7 N sulfuric acid being omitted. The limit is 8 µg per g.

Chloride—

Test solution—Dissolve 0.5 g in 20 mL of sodium hydroxide TS by boiling. Allow to cool, and filter, if necessary, to obtain a clear solution. Wash the filter with 10 mL of water. Combine the filtrate and the washing, add 18 mL of dilute nitric acid, and add water to make 50 mL.

Standard solution—To 0.35 mL of 0.010 N hydrochloric acid VS add 20 mL of sodium hydroxide TS and 18 mL of dilute nitric acid, and dilute with water to 50 mL.

Procedure—To the *Test solution* and the *Standard solution* add 1 mL of silver nitrate TS, mix, and allow to stand for 5 minutes, protected from direct sunlight. The opalescence, if any, developed in the *Test solution* is not more than that in the *Standard solution* (0.025%).

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Bulk density—Place a No. 70 sieve (212 μm) at a position of about 20 cm above a tared brass or stainless steel cup, which has the capacity of 25.0 ± 0.05 cm^3 and an inside diameter of 30.0 ± 2.0 mm. Slowly pour Colloidal Silicon Dioxide through the sieve, at a rate suitable to prevent clogging until the cup overflows. Level the excess powder with the aid of a slide glass, weigh the filled cup, weigh accurately the content of the cup, and then calculate the bulk density by the following expression: the bulk density is within the labeled specification.

$$\text{Bulk density } (g/cm^3) = A/25$$

where A is the measured mass of the content of the cup (g).

Assay—Accurately weigh and transfer about 0.5 g *(m)* of Colloidal Silicon Dioxide, that has been previously ignited at 1000° for 2 hours, to a tared platinum dish (previously ignited at 1000° for 30 minutes), weigh the dish, and designate the mass as a (g). Moisten the sample with 4 drops of alcohol and 2 drops of sulfuric acid, add 15 mL of hydrofluoric acid, and evaporate to dryness on a water bath with a well-ventilated hood. After cooling, add about 5 mL of hydrofluoric acid, and evaporate to dryness. Heat the residue at 550° for 1 hour, gradually increasing the temperature, and ignite at 1000° for 30 minutes. Cool in a desiccator, weigh the dish, and designate the mass as b (g). Calculate the percentage of SiO_2 using the following formula:

$$[(a - b)/m] \times 100$$

GENERAL CHAPTERS

General Tests and Assays

Chemical Tests and Assays

OTHER TESTS AND ASSAYS

BRIEFING

⟨**429**⟩ **Light Diffraction Measurement of Particle Size.** *USP 28* page 2314 and page 895 of *PF* 28(3) [May–June 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this chapter. This proposal represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **STAGE 3** draft that appeared in *Harmonization* on page 895 of PF 28(3) [May–June 2002]. The proposed chapter is based on ISO Standards 13320-1 (1999) and 9276-1 (1998) and better reflects the main purpose of the method: monitoring batch-to-batch variability, rather than achieving absolute accuracy for the sphere-equivalent diameter. The use of the Mie theory and the Fraunhofer approximation is described more fully. This compromise should cover all comments without being too restrictive, and it provides a general guide about the often-debated topic of Fraunhofer versus Mie. Although the chapter is based on the ISO guide (0.1 to 3 mm), the range of applicability (e.g., 0.1 to 8 mm) is left open for new advances in lenses, detectors, and constructions. In *Evaluation of the Dispersion Procedure,* the sentence ''Moreover, if the manufacturing process (e.g., crystallization, milling) of the material has changed, the applicability of the method must be verified (e.g., microscopic comparison)'' has been included. In addition, in *Conversion of the Scattering Pattern into Particle Size Distribution,* the following sentences have been added: ''The algorithms used are specific to each make and model of equipment and are proprietary. The differences in the algorithms between different instruments may give rise to differences in the calculated particle size statistics.'' In the same section, to fully describe the possibilities of the existence of differences between equipment (other than random and systematic errors), the following sentence has also been added: ''The assumption of spherical particle shape is particularly important, because most algorithms use the mathematical solution for scattering from spherical particles.'' Other minor changes and editorial

changes are also included. Readers are requested to review the proposal carefully and to send comments to USP; the deadline for receipt is **30 September 2005.**

(ETM: J. Lane) RTS—42307-3

Add the following:

⟨429⟩ LIGHT DIFFRACTION MEASUREMENT OF PARTICLE SIZE

The laser light diffraction technique used for the determination of the particle size distribution is based on the analysis of the diffraction pattern produced when particles are exposed to a beam of coherent light. Historically, the early laser diffraction instruments used only scattering at small angles. However, the technique has since been broadened to include laser light scattering in a wider angular range and application of the Mie theory in addition to the Fraunhofer approximation and anomalous diffraction. Moreover, new measuring principles with incoherent light source modulated by a liquid crystal display and a photo-multiplier detector are available.

The technique cannot distinguish between scattering by single particles and scattering by clusters of primary particles, i.e., by agglomerates or aggregates. As most particulate samples contain agglomerates or aggregates and as one is generally interested in the size distribution of primary particles, the clusters are usually dispersed into primary particles before measurement.

For nonspherical particles, an equivalent sphere size distribution is obtained because the technique assumes spherical particles in its optical model. The resulting particle size distribution may differ from those obtained by methods based on other physical principles (e.g., sedimentation, sieving).

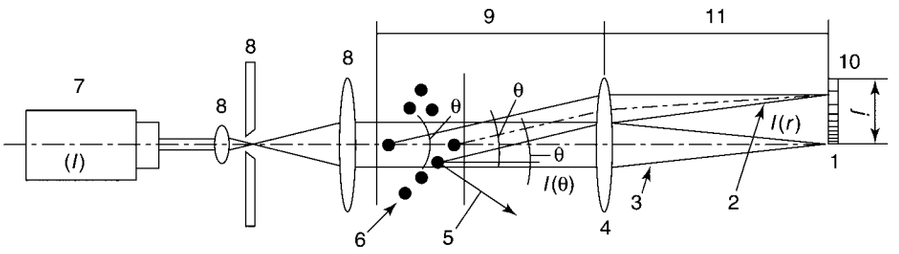
This chapter provides guidance for the measurement of size distributions of particles in different dispersed systems—for example, powders, sprays, aerosols, suspensions, emulsions and gas bubbles—in liquids through analysis of their angular light scattering patterns. It does not address specific requirements of particle size measurement of specific products.

PRINCIPLE

A representative sample, dispersed at an adequate concentration in a suitable liquid or gas, is passed through a beam of monochromatic light, usually a laser. The light scattered by the particles at various angles is measured by a multielement detector. Numerical values representing the scattering pattern are then recorded for subsequent analysis. These scattering pattern 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.

APPARATUS

A typical setup for a laser diffraction instrument is shown in *Figure 1.*



1. Obscuration detector
2. Scattered beam
3. Direct beam
4. Fourier lens
5. Scattered light not collected by lens (4)
6. Particle ensemble
7. Light source laser
8. Beam processing unit
9. Working distance of lens (4)
10. Multi-element detector
11. Focal distance of lens (4)

Figure 1. Typical setup for a laser diffraction instrument.

The instrument comprises a laser light source, beam processing optics, a sample measurement region (or cell), a Fourier lens, and a multi-element detector for measuring the scattered light pattern. A data system is also required for deconvolution of the scattering data into a volumetric size distribution and associated data analysis and reporting.

The particles can enter the laser beam in two positions. In the conventional case the particles enter the parallel beam before and within the working distance of the collecting lens. In so-called reversed Fourier optics 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 submicron particles are present.

The interaction of the incident light beam and the ensemble of 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 lens or a series of lenses onto a multi-element detector. The lens(es) create(s) a scattering pattern which, within limits, does not depend on the location of the particles in the light beam. Hence, the continuous angular intensity distribution is converted into a discrete spatial intensity distribution on a set of detector elements.

It is assumed that the measured 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, therefore, by the detector.

DEVELOPMENT OF THE METHOD

Traditionally, the measurement of particle size using laser diffraction has been limited to particles in the range from approximately 0.1 μm to 3 mm. Because of recent advances in lens and equipment design, newer instruments are capable of exceeding this range routinely (e.g., 0.1 μm to 8 mm). With the validation report the user demonstrates the applicability of the method for its intended use.

Sampling

The sampling technique must be adequate to obtain a representative sample of a suitable volume for the particle size measurement.

Evaluation of the Dispersion Procedure

The dispersion procedure must be adjusted to the purpose of the measurement. The purpose may be such that it is preferable to deagglomerate clusters into primary particles as far as possible, or it may be desirable to keep clusters as intact as possible. In this sense, the particles of interest may be either primary particles or clusters.

For the development of a method it is highly advisable to check that comminution of the particles is minimized, and conversely, that dispersion of particles or clusters is satisfactory. This can usually be done by changing the dispersing energy and monitoring the change of the particle size distribution. The measured size distribution must not change significantly when the sample is well dispersed and the particles are neither fragile nor soluble. In addition, the particles of interest can be inspected visually or with the aid of a microscope. Moreover, if the manufacturing process (e.g., crystallization, milling) of the material has changed, the applicability of the method must be verified (e.g., microscopic comparison).

Sprays, aerosols, and gas bubbles in a liquid should be measured directly, provided that their concentration is adequate, because sampling or dilution generally alters the particle size distribution.

In other cases (as with emulsions, pastes, and powders), representative samples may be dispersed in suitable liquids. Often dispersing aids (wetting agents, stabilizers) and/or mechanical forces (e.g., agitation, ultrasonication) are applied for deagglomeration or deaggregation of clusters and stabilization of the dispersion. For these liquid dispersions, a recirculating system is most commonly used, consisting of an optical measuring cell; a dispersion bath, usually equipped with stirrer and ultrasonic elements; a pump; and tubing. Nonrecirculating, stirred cells are useful when only small amounts of a sample are available or when special dispersion liquids are used.

Dry powders can also be converted into aerosols through the use of suitable dry powder dispersers, which apply mechanical force for deagglomeration or deaggregation. Generally the dispersers use the energy of compressed gas or the differential pressure of a vacuum to disperse the particles to an aerosol, which is blown through the measuring zone, usually into the inlet of a vacuum unit that collects the particles. However, for free-flowing, coarser particles or granules, the effect of gravity may be sufficient to disperse the particles adequately.

Optimization of the Liquid Dispersion

Liquids, surfactants, and dispersing aids used to disperse powders must

- be transparent at the laser wavelength and practically free from air bubbles or particles;
- have a refractive index that differs from that of the test material;
- be nonsolvent of the test material (pure liquid or pre-filtered saturated solution);
- not alter the size of the test materials (e.g., by solubility, solubility enhancement, or recrystallization effects);
- favor easy formation and stability of the dispersion;
- be compatible with the materials used in the instrument (such as O-rings, gaskets, tubing, etc.); and
- possess a suitable viscosity to facilitate recirculation, stirring, and filtration.

Quite often, surfactants and/or dispersing aids are used to wet the particles and to stabilize the dispersion. For weak acids and weak bases, buffering of the dispersing medium at a low or a high pH, respectively, can assist in identifying a suitable dispersant.

The quality of a dispersion can be checked preliminarily by visual or microscopic inspection. It is also possible to take fractional samples out of a well-mixed stock dispersion. Such stock dispersions are formed by adding a liquid to the sample while mixing it with, for example, a glass rod, a spatula, or a vortex mixer. Care must be taken to ensure a representative transfer of the sample and to ensure that settling of larger particles does not occur.

Optimization of the Gas Dispersion

For dry dispersion and sprays, a compressed gas free from oil, water, and particles may be used. To remove such materials from the compressed gas, a dryer with a filter can be used. Any vacuum unit should be located away from the measurement zone so that its output does not disturb the measurement.

Determination of the Concentration Range

In order to produce an acceptable signal-to-noise ratio in the detector, the particle concentration in the dispersion must exceed a minimum level. Likewise, it must be below a maximum level in order to avoid multiple scattering. The concentration range is influenced by the width of the laser beam, 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, measurements must be performed at different particle concentrations to determine the appropriate concentration range for any typical sample of material. [NOTE—In different instruments, particle concentrations are usually represented by differently scaled and differently named numbers (e.g., obscuration, optical concentration, proportional number of total mass).]

Selection of an Appropriate Optical Model

Most instruments use either the Fraunhofer approximation or the Mie theory, although other approximation theories are sometimes applied for calculation of the scattering matrix. The choice of the theoretical model depends on the intended application by the user and the different assumptions (e.g., size, absorbance, refractive index, roughness, crystal orientation, mixture) made for the test material. If the refractive index values (real and imaginary parts for the wavelength used) are not exactly known, then the Fraunhofer approximation or the Mie theory with a realistic estimate of the refractive index can be used. The former has the advantages that it is simple, it does not need refractive index values, and it is extremely useful for analysis of powders coarser than about 1–2 μm; the latter usually provides less biased particle size distributions for small particles. In order to obtain traceable results, it is essential to document the refractive index values used, because small differences in the values assumed for the real and imaginary part of the complex refractive index may cause significant differences in the measured particle size distributions. Small values of the imaginary part of the refractive index (about 0.01i–0.1i) are often applied to allow the correction of the absorbance for the surface roughness of the particles.

Repeatability

The attainable repeatability of the method mainly depends on the characteristics of the material (milled/not milled, robust/fragile, width of its size distribution, etc.), whereas the required repeatability depends on the purpose of the measurement. Mandatory limits cannot be specified because repeatabilities (different sample preparations) may strongly vary from one substance to another. However, it is good practice to aim at acceptance criteria for repeatability like $s_{rel} \leq 10\%$ [$n = 6$] for any central value of the distribution (e.g.,

for x_{50}). Values at the trailing sides of a distribution (e.g., x_{10} and x_{90}) are oriented toward less stringent acceptance criteria like $s_{rel} \leq 15\%$ [$n = 6$]. Below 10 µm, these values must be doubled.

MEASUREMENT

Precautions

The instructions given in the apparatus manual are followed:

- Never look into the direct path of the laser beam or its reflections;
- ground all apparatus components to prevent ignition of solvents or dust explosions;
- check the apparatus setup (e.g., warm-up, required measuring range and lens, appropriate working distance, position of the detector, no direct bright daylight);
- in the case of wet dispersions, avoid air bubbles, evaporation of liquid, and schlieren or other inhomogeneities in the dispersion. Similarly, avoid improper mass flow from the disperser or turbulent airflow in the case of dry dispersions. Such effects can cause erroneous particle size distributions.

Measurement of the Scattering of Dispersed Sample(s)

After proper alignment of the optical part of the instrument, a blank measurement of the particle-free dispersion medium must be performed. The background signal must be below an appropriate threshold.

Generally, the time for measurement permits a large number of detector scans or sweeps at short time intervals. For each detector element, an average signal is calculated, sometimes together with its standard deviation. The magnitude of the signal from each detector element depends on 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 range of scattering angles for each element. Most instruments also measure the intensity of the central (unscattered) laser beam. The ratio of the intensity of a dispersed sample to that in its absence (a blank measurement) indicates the proportion of scattered light and hence the particle concentration.

Conversion of the 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 assumption of spherical particle shape is particularly important, because most algorithms use the mathematical solution for scattering from spherical particles. Furthermore, the measured data always contain some random and systematic errors that may vitiate the size distributions. Several mathematical procedures have been developed for use in the available instruments. They contain some weighting of deviations between measured and calculated scattering patterns (e.g., least squares), some constraints (e.g., non-negativity for amounts of particles), and/or some smoothing of the size distribution curve. The algorithms used are specific to each make and model of equipment and are proprietary. The differences in the algorithms between different instruments may give rise to differences in the calculated particle size statistics.

Replicates

It is recommended that the number of replicate measurements (with individual sample preparations) to be performed per sample, in a substance-specific method, be defined.

REPORTING OF RESULTS

The particle size analysis data are usually reported as cumulative undersize distribution by volume. The symbol x is used to denote the particle size, which in turn is defined as the diameter of a volume equivalent sphere. *Q3(x)* denotes the volume fraction undersize at the particle size x. In a graphical representation, x is plotted on the abscissa and the dependent variable *Q3* on the ordinate. Most common characteristic values are calculated from the particle size distribution by interpolation. Frequently used are the particle sizes at the undersize values of 10%, 50%, and 90%, denoted as x_{10}, x_{50}, and x_{90}, respectively. The size x_{50} is also known as the median particle size. It is recognized that the symbol d is also widely used to designate the particle size; thus the symbol x may be replaced by d.

Moreover, sufficient information must be documented about the sample, the sample preparation, the dispersion conditions, and cell type. Becauses the results depend on the particular instrument, data analysis program, and optical model used, the respective information must also be documented.

CONTROL OF THE APPARATUS PERFORMANCE

Use the apparatus according to the manufacturer's instructions and carry out the prescribed verifications at appropriate frequency, according to the use of the apparatus and substances to be tested.

Calibration

Laser diffraction systems are based on first principles of laser light scattering, although assuming idealized properties of the particles. Thus, calibration in the strict sense is not required. However, it is still necessary to confirm that the instrument is operating correctly. This can be undertaken using any certified or standard reference material acceptable in industrial practice. The entire measurement procedure is examined, including sample collection, sample dispersion, sample transport through the measuring zone, measurement, and the deconvolution procedure. It is essential that the total operational procedure be fully described.

The preferred certified or standard reference materials consist of spherical particles of a known distribution ranging over one decade of size. They must be certified as to the mass percentage size distribution by an absolute technique, if available, and used in conjunction with an agreed-upon, detailed operation procedure. It is essential that the real and imaginary parts of the complex refractive index of the material be indicated if the Mie theory is applied in data analysis. The representation of the particle size distribution by volume will equal that of the distribution by mass, provided that the density of the particles is the same for all size fractions.

The response of a laser diffraction instrument is considered to meet the requirements if the mean value of x_{50} from at least three independent measurements does not deviate by more than 3% from the certified range of values of the certified or standard reference material; that is, the mean value together with its standard deviation. The mean values for x_{10} and x_{90} must not deviate by more than 5% from the certified range of values. For repeatability, the coefficient of variation must not exceed 3% for x_{50} and 5% for x_{10} and x_{90}. Below 10 μm, these values must be doubled.

Although use of materials consisting of spherical particles is preferable, nonspherical particles may also be employed. Preferably, these particles have certified or typical values from laser diffraction analyses performed according to an agreed-upon, detailed operating procedure. Use of reference values from methods other than laser diffraction may cause

a significant bias. The reason for this bias is that the different principles inherent in the various methods may lead to different sphere-equivalent diameters for the same nonspherical particle.

In addition to the certified reference materials mentioned above, product samples of typical composition and particle size distribution for a specified class of products can also be used, provided their particle size distribution has proven to be stable over time. The results must comply with previously determined data with the same precision and bias as those for the certified reference material.

Verification of the System

In addition to the calibration, the performance of the apparatus must be verified at regular time intervals or as frequent as appropriate. This can be undertaken using any suitable material as mentioned in the previous paragraph.

The verification of the system is based on the concept that the equipment, electronics, software and analytical operations constitute an integral system, which can be evaluated as an entity. Thus the entire measurement procedure is examined, including sample collection, sample dispersion, sample transport through the measuring zone, and the measurement and deconvolution procedure. It is essential that the total operational procedure is fully described.

In the general case, unless otherwise specified in the individual monograph, the response of a laser diffraction instrument is considered to meet the requirements if the x_{50} value does not deviate by more than 10% from the range of values of the reference material, i.e., the mean value together with its standard deviation. If optionally the values at the trailing sides of the distribution are evaluated (e.g., x_{10} and x_{90}), then these values must not deviate by more than 15% from the certified range of values. Below 10 μm, these values must be doubled.

Physical Tests and Determinations

BRIEFING

⟨**941**⟩ **X-Ray Diffraction.** *USP 28* page 2513. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this chapter. This proposal represents the **OFFICIAL INQUIRY STAGE 4** draft in the harmonization process, based in part on comments received in response to the **STAGE 3** draft. The proposal elaborates on the USP chapter. New figures are added, and multiple footnotes are added for clarity. Other changes, including minor editorial changes, have been made. Readers are requested to review the proposal carefully and to send comments to USP; the deadline for receipt is **30 September 2005.**

(ETM: J. Lane) RTS—42308-1

Add the following:

⟨941⟩ X-RAY DIFFRACTION

Every crystalline phase of a given substance produces a characteristic X-ray diffraction pattern. Diffraction patterns can be obtained from a randomly oriented crystalline powder composed of crystallites or crystal fragments of finite size of the substance. Essentially three types of information can be derived from a powder diffraction pattern: the angular position of diffraction lines (depending on geometry and size of the unit cell), the intensities of diffraction lines (depending mainly on atom type and arrangement and particle orientation within the sample), and diffraction line profiles (depending on instrumental resolution, crystallite size, strain, and specimen thickness).

Experiments giving angular positions and intensities of lines can be used for applications such as qualitative phase analysis (e.g., identification of crystalline phases) and quantitative phase analysis of crystalline materials. An estimate of the amorphous and crystalline fractions[1] can also be made.

In addition, analysis of line profile broadening can also allow for determination of crystallite size (size of coherently scattering domains) and micro-strain.

The X-ray powder diffraction (XRPD) method provides an advantage over other means of analysis in that it is usually nondestructive in nature (to ensure a randomly oriented sample, specimen preparation is usually limited to grinding). XRPD investigations can also be carried out under in situ conditions on specimens exposed to nonambient conditions such as low or high temperature and humidity.

PRINCIPLES

X-ray diffraction results from the interaction between X-rays and electron clouds of atoms. Depending on atomic arrangement, interferences arise from the scattered X-rays. These interferences are constructive when the path difference between two diffracted X-ray waves differs by an integral number of wavelengths. This selective condition is described by the Bragg equation, also called Bragg's law *(Figure 1).*

$$2d_{hkl}\sin\theta_{hkl} = n\lambda$$

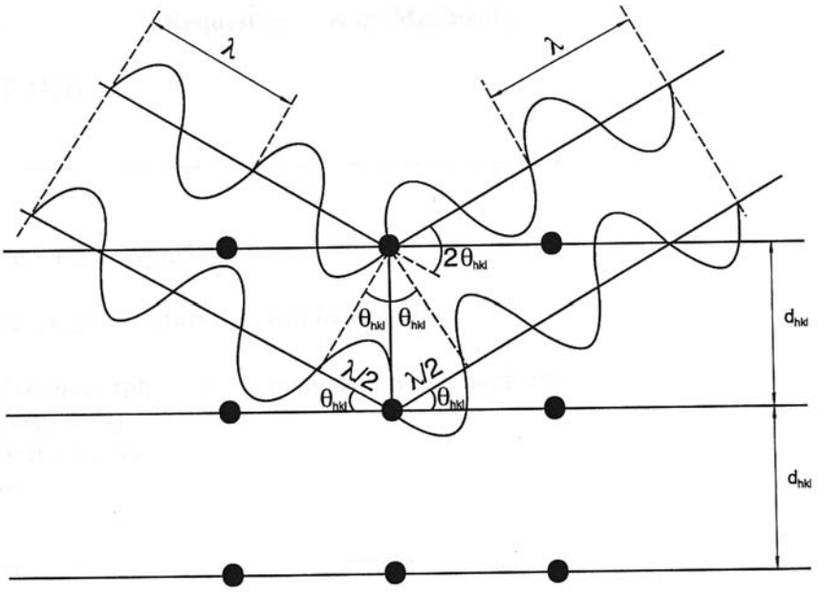


Figure 1. Diffraction of X-rays by a crystal according to Bragg's law.

[1] There are many other applications of the X-ray powder diffraction technique that can be applied to crystalline pharmaceutical substances, such as determination of crystal structures, refinement of crystal structures, determination of the crystallographic purity of crystalline phases, and characterization of crystallographic texture. These applications are not described in this chapter.

The wavelength, λ, of the X-rays is of the same order of magnitude as the distance between successive crystal lattice planes, or d_{hkl} (also called *d*-spacings). θ_{hkl} is the angle between the incident ray and the family of lattice planes, and $\sin\theta_{hkl}$ is inversely proportional to the distance between successive crystal planes or *d*-spacings.

The direction and spacing of the planes with reference to the unit cell axes are defined by the Miller indices {*hkl*}. These indices are the reciprocals, reduced to the smallest integers, of the intercepts that a plane makes with the unit cell axes. The unit cell dimensions are given by the spacings *a*, *b,* and *c,* and the angles between them by α, β, and γ.

The interplanar spacing for a specified set of parallel *hkl* planes is denoted by d_{hkl}. Each such family of planes may show higher orders of diffraction where the *d* values for the related families of planes *nh, nk, nl* are diminished by the factor 1/*n* (*n* being an integer: 2, 3, 4, etc.).

Every set of planes throughout a crystal has a corresponding Bragg diffraction angle, θ_{hkl}, associated with it (for a specific λ).

A powder specimen is assumed to be polycrystalline so that at any angle θ_{hkl} there are always crystallites in an orientation allowing diffraction according to Bragg's law.[2] For a given X-ray wavelength, the positions of the diffraction peaks (also referred to as ''lines'', ''reflections'', or ''Bragg reflections'') are characteristic of the crystal lattice (*d*-spacings), their theoretical intensities depend on the crystallographic unit cell content (nature and positions of atoms), and the line profiles depend on the perfection and extent of the crystal lattice. Under these conditions, the diffraction peak has a finite intensity arising from atomic arrangement, thermal motion, and structural imperfections, as well as from instrument characteristics.

The main characteristics of diffraction line profiles are 2θ position, peak height, peak area, and shape (characterized by, e.g. peak width, asymmetry or by analytical function, empirical representation). An example of the type of powder patterns obtained for five different solid phases of a substance[3] are shown in *Figure 2.*

[2] An ideal powder for diffraction experiments consists of a large number of small, randomly oriented spherical crystallites (coherently diffracting crystalline domains). If this number is sufficiently large, there are always enough crystallites in any diffracting orientation to give reproducible diffraction patterns. To obtain a precise measurement of the intensity of diffracted X-rays, it is recommended that the crystallite size be small—that is, typically 10 μm or less, depending on the characteristics of the specimen (X-ray absorption, shape, etc.) and the diffraction geometry.

[3] These diffraction patterns were collected on a Siemens D500 diffractometer (Bragg-Brentano geometry) using a pure monochromatic CuKα1 radiation (λ = 0.1540598 nm) selected with an incident-beam curved-crystal germanium monochromator with asymmetric focusing (short focal distance 124 mm, long focal distance 216 mm). Detection of signal was achieved using a scintillation detector. To reduce the effect of transparency of the specimens, a thin layer of powder was deposited on an oriented single crystal silicon wafer. The alignment of the diffractometer was checked by means of the OOI reflections of fluorophlogopite mica (NIST SRM 675). The zero error was estimated as less than 0.01° (2θ). The instrumental resolution function of the setup exhibits a shallow minimum of 0.065° (2θ) at about 40° (2θ) and has twice this value at 130° (2θ). For each phase, the diffraction pattern was scanned with the same step length of 0.02° (2θ), but with different fixed counting times [form A: 30 seconds; form B: 48 seconds; form C: 48 seconds; form D: 40 seconds; amorphous phase: 10 seconds].

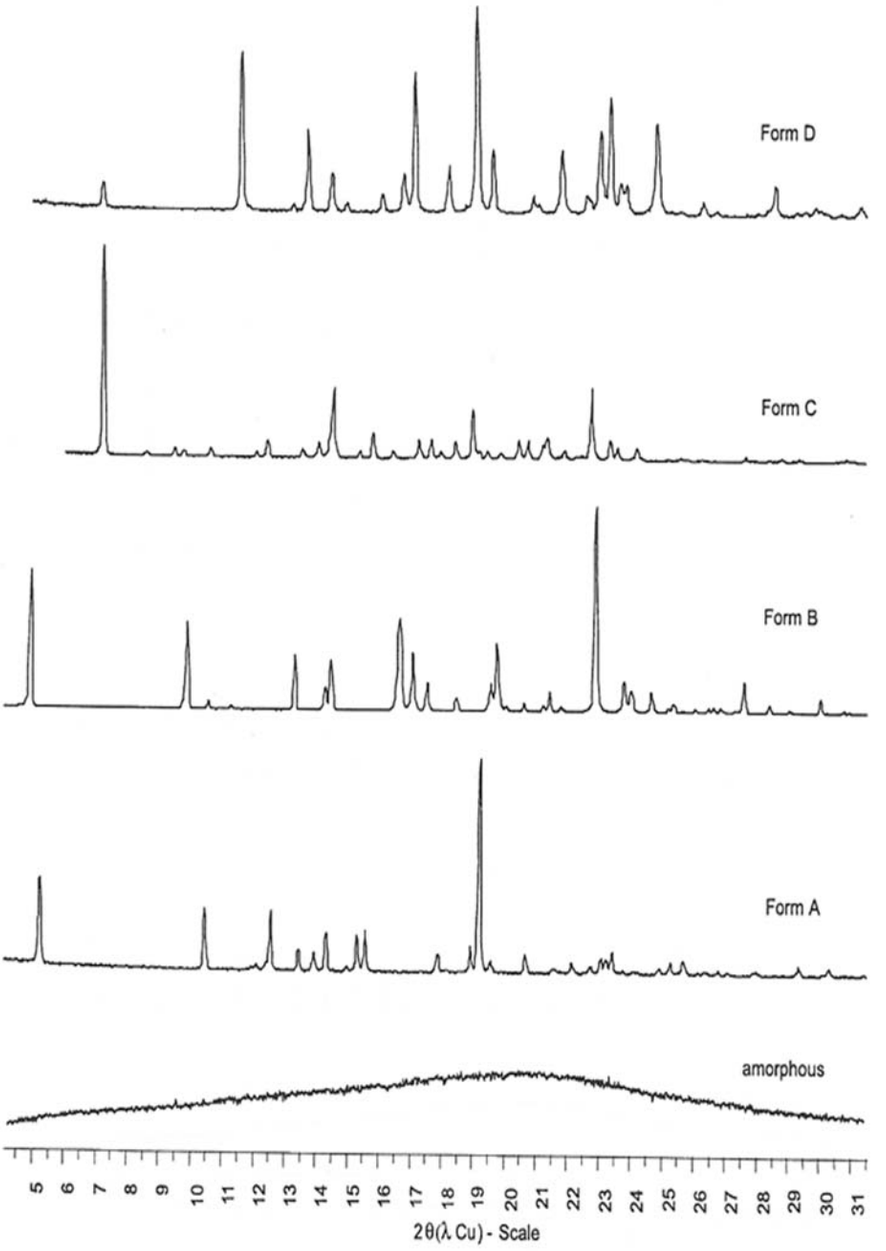


Figure 2. X-ray powder patterns collected for five different solid phases of a substance. The intensities are normalized.

In addition to the diffraction peaks, an X-ray diffraction experiment also generates a more or less uniform background, upon which the peaks are superimposed. Besides specimen preparation, other factors contribute to the background—for example, sample holder, diffuse scattering from air and equipment, other instrumental parameters such as detector noise, and general radiation from the X-ray tube. The peak-to-background ratio can be increased by minimizing background and by choosing prolonged exposure times.

APPARATUS

Instrument Setup

X-ray diffraction experiments are usually performed using powder diffractometers or powder cameras.

A powder diffractometer generally comprises five main equipment parts: an X-ray source; the incident beam optics, which may include monochromatization, filtering, collimation, and/or focusing of the beam; a goniometer; the diffraction beam optics, which may include monochromatization, filtering, collimation, and focusing or parallelizing of beam; and a detector. Data collection and data processing systems are also required and are generally included in current diffraction measurement equipment.

Depending on the type of analysis to be performed (phase identification, quantitative analysis, lattice parameters determination, etc.), different XRPD instrument configurations and performance levels are required. The simplest instruments used to measure powder patterns are powder cameras. Of the various camera types available, three are commonly employed: the Debye-Scherrer, the Gandolfi, and the Guinier focusing cameras. Replacement of photographic film by photon detectors as a detection method has led to the design of diffractometers in which the geometric arrangement of the optics is not truly focusing, but parafocusing, as in Bragg-Brentano geometry. The Bragg-Brentano parafocusing configuration is currently the most widely used and is therefore briefly described here.

A given instrument may provide a horizontal or vertical $\theta/2\theta$ geometry or a vertical θ/θ geometry. For both geometries, the incident X-ray beam forms an angle θ with the specimen plane, and the diffracted X-ray beam forms an angle 2θ with the direction of the incident X-ray beam (an angle θ with the specimen plane). The basic geometric arrangement is represented in *Figure 3*. The divergent beam of radiation from the X-ray tube (the so-called primary beam) passes through the parallel plate collimators and a divergence slit assembly and illuminates the flat surface of the specimen. All the rays diffracted by suitably oriented crystallites in the specimen at an angle 2θ converge to a line at the receiving slit. A second set of parallel plate collimators and a scatter slit may be placed either behind or before the receiving slit. The axes of the line focus and of the receiving slit are at equal distances from the axis of the goniometer. The X-ray quanta are counted by a radiation detector, usually a scintillation counter, a sealed-gas proportional counter, or a position-sensitive detector or solid-state detector. The receiving slit assembly and the detector are coupled together and move tangentially to the focusing circle. For $\theta/2\theta$ scans, the goniometer rotates the specimen around the same axis as that of the detector, but at half the rotational speed, in a $\theta/2\theta$ motion. The surface of the specimen thus remains tangential to the focusing circle. The parallel plate collimator limits the axial divergence of the beam and hence partially controls the shape of the diffracted line profile.

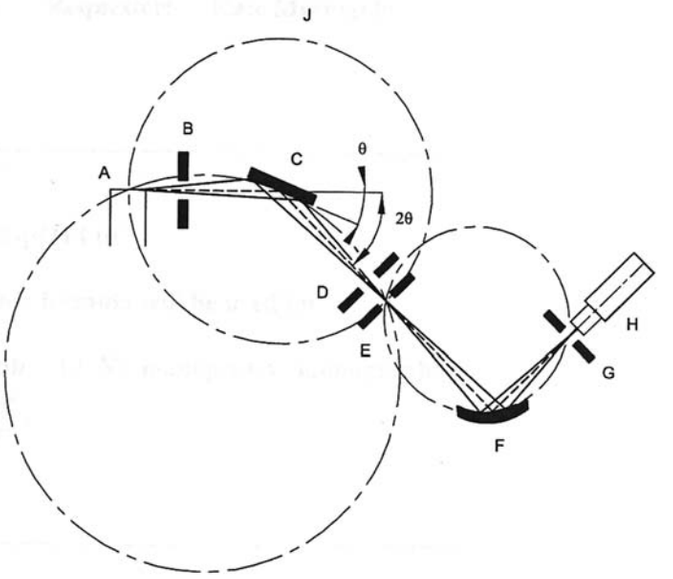


Figure 3. Diffraction of X-rays by a crystal according to Bragg's law.

A Bragg-Brentano diffractometer may also be used in transmission mode. The advantage with this technology is that there are fewer effects of the preferred orientation. A mounted capillary of about 0.5–2 mm thickness can also be used for small sample amounts.

X-Ray Radiation

In the laboratory, X-rays are obtained by bombarding a metal anode with electrons emitted by the thermionic effect and accelerated in a strong electric field (using a high-voltage generator). Most of the kinetic energy of the electrons is converted to heat, which limits the power of the tubes and requires efficient anode cooling. A 20- to 30-fold increase in brilliance can be obtained by using rotating anodes and by using X-ray optics. Alternatively, X-ray photons may be produced in a large-scale facility (synchrotron).

The spectrum emitted by an X-ray tube operating at sufficient voltage consists of a continuous background of polychromatic radiation and additional characteristic radiation that depends on the type of anode. Only this characteristic radiation is used in X-ray diffraction experiments. The principal radiation sources used for X-ray diffraction are vacuum tubes using copper, molybdenum, iron, cobalt, or chromium as anodes; copper, molybdenum, or cobalt X-rays are employed most commonly for organic substances (the use of a cobalt anode can especially be preferred to separate distinct X-ray lines). The choice of radiation to be used depends on the absorption characteristics of the specimen and possible fluorescence by atoms present in the specimen. The wavelengths used in powder diffraction generally correspond to the K_α radiation from the anode. Consequently, it is advantageous to make the X-ray beam "monochromatic" by eliminating all the other components of the emission spectrum. This can be partly obtained using

K_β filters—that is, metal filters selected as having an absorption edge between the K_β and K_α wavelengths emitted by the tube. Such a filter is usually inserted between the X-ray tube and the specimen. Another more commonly used way to obtain a monochromatic X-ray beam is via a large monochromator crystal (usually referred to as a "monochromator"). This crystal is placed before or behind the specimen and diffracts the different characteristic peaks of the X-ray beam (i.e., K_β and K_α) at different angles so that only one of them may be selected to enter into the detector. It is even possible to separate $K_{\alpha1}$ and $K_{\alpha2}$ radiations by using a specialized monochromator. Unfortunately, the gain in getting a monochromatic beam by using a filter or a monochromator is counteracted by a loss in intensity. Another way of separating K_α and K_β wavelengths is by using curved X-ray mirrors that can simultaneously monochromate and focus or parallelize the X-ray beam.

Radiation Protection

Exposure of any part of the human body to X-rays can be injurious to health. It is therefore essential that whenever X-ray equipment is used, adequate precautions be taken to protect the operator and any other person in the vicinity. Recommended practice for radiation protection and limits to levels of X-radiation exposure are those established by national legislation in each country. If there are no official regulations or recommendations in a country, the latest recommendations of the International Commission on Radiological Protection should be applied.

SPECIMEN PREPARATION AND MOUNTING

The preparation of the powdered material and the mounting of the specimen in a suitable holder are critical steps in many analytical methods, particularly for X-ray powder diffraction analysis, because preparation and mounting can greatly affect the quality of the data to be collected.[4] The main sources of errors due to specimen preparation and mounting are briefly discussed in the following section for instruments in Bragg-Brentano parafocusing geometry.

SPECIMEN PREPARATION

In general, the morphology of many crystalline particles tends to produce a specimen that exhibits some degree of preferred orientation in the specimen holder. This is particularly evident for needle-like or platelike crystals when size reduction yields finer needles or platelets. Preferred orientation in the specimen influences the intensities of various reflections so that some are more intense and others less, compared to what would be expected from a completely random specimen. Several techniques can be employed to improve randomness in the orientation of crystallites (and therefore to minimize preferred orientation), but further reduction of particle size is often the best and simplest approach. The optimum number of crystallites depends on the diffractometer geometry, the required resolution, and the specimen attenuation of the X-ray beam. In some cases, particle sizes as large as 50 μm will provide satisfactory results in phase identification. For quantitative XRPD analysis, it is often recommended that the specimen have coherent domains (crystallites) with a size < 10 μm. However, excessive milling (crystallite sizes approximately < 0.5 μm) may cause line broadening and significant changes to the sample itself, such as the following:

- specimen contamination by particles abraded from the milling instruments (mortar, pestle, balls, etc.),
- reduced degree of crystallinity,
- solid-state transition to another polymorph,
- chemical decomposition,

[4] Similarly, changes in the specimen can occur during data collection in the case of a nonequilibrium specimen (temperature, humidity).

- introduction of internal stress, and
- solid-state reactions.

Therefore, it is advisable to compare the diffraction pattern of the nonground specimen with that corresponding to a specimen of smaller particle size (e.g., a milled specimen). If the X-ray powder pattern obtained is of adequate quality considering its intended use, then grinding may not be required.

It should be noted that if a sample contains more than one phase and if sieving is used to isolate particles to a specific size, the initial composition may be altered.

SPECIMEN MOUNTING

Effect of Specimen Displacement

A specimen surface that is offset by D with reference to the diffractometer rotation axis[5] causes systematic errors that are very difficult to avoid entirely, resulting in absolute $D \cdot \cos\theta$ shifts[6] in 2θ positions (typically of the order of 0.01° in 2θ at low angles [$\cos\theta \cong 1$] for a displacement D = 15 μm) and asymmetric broadening of the profile toward low 2θ values. Use of an appropriate internal standard allows the detection and correction of this effect simultaneously with that arising from specimen transparency. This effect is by far the largest source of errors in data collected on well-aligned diffractometers.

Effect of Specimen Thickness and Transparency

When the XRPD method in reflection mode is applied, it is often preferable to work with specimens of ''infinite thickness''. This means that, for a given mass attenuation and bulk density of the specimen and a given range of diffraction angles, the diffracted intensity from the back of the specimen is negligible. For quantitative analysis, to ensure that the diffracted intensity is at least 99.9% of the maximum attainable by increasing the specimen thickness, *t,* the thickness, must be at least:

$$t = 3.45\sin\theta/\mu'\rho'$$

where μ' is the mass attenuation coefficient (often referred to as the mass absorption coefficient) and ρ' is the bulk density of the specimen. μ' is additive for the mass attenuation coefficients of the individual elements that constitute the material. It is independent of the physical state of the material.

For specimens with low attenuation (such as organic materials where the linear absorption coefficients are very small), the diffracted intensity appears to originate from a position below the surface, resulting in line shifts and changes in line widths. This effect, referred to as the transparency effect, is large for thick specimens with low attenuation and can lead to angular errors of as much as 0.1°. For such specimens, a precise measurement of line positions can be carried out on a specimen that is as thin as possible, but that still gives acceptable diffraction intensities. It is advisable to use a nondiffracting substrate (zero background holder)—for example, a plate of single crystalline silicon cut parallel to the 510 lattice planes.[7] One advantage of the transmission mode is that problems with sample height and specimen transparency are less important.

Use of an appropriate internal standard allows the detection and correction of this effect simultaneously with that arising from specimen displacement.

[5] D is the specimen surface displacement (offset of the specimen surface with reference to the diffractometer axis).

[6] Note that a goniometer zero alignment shift would result in a constant shift on all observed 2θ-line positions; in other words, the whole diffraction pattern is, in this case, translated by an offset of Z° in 2θ.

[7] In the case of a thin specimen with low attenuation, accurate measurements of line positions can be made with focusing diffractometer configurations in either transmission or reflection geometry. Accurate measurements of line positions on specimens with low attenuation are preferably made using diffractometers with parallel beam optics. This helps to reduce the effects of specimen thickness.

DIFFRACTOMETER ALIGNMENT

Goniometers and the corresponding incident and diffracted X-ray beam optics have many mechanical parts that need adjustment. The degree of alignment or misalignment directly influences the quality of the results of an XRPD investigation. Therefore, the different components of the diffractometer must be carefully adjusted (optical and mechanical systems, etc.) to adequately minimize systematic errors, while optimizing the intensities received by the detector. The search for maximum intensity and maximum resolution is always antagonistic when aligning a diffractometer. Hence, the best compromise must be sought while performing the alignment procedure. There are many different configurations, and each supplier's equipment requires specific alignment procedures.

CALIBRATION, PERFORMANCE TESTING, AND MONITORING OF DIFFRACTOMETERS

To establish the magnitude of potential errors in the diffractometer, a calibration curve, using a proper calibrant, whether internal or external, can be prepared after the alignment of the diffractometer for each of the following: angular calibration, intensity calibration, and line shape calibration. Calibration is usually performed using certified reference standards (the choice depends on the type of analysis). The overall diffractometer performance should be tested and monitored periodically, using working standards and/or reference standards (depending on the type of analysis).

QUALITATIVE PHASE ANALYSIS (IDENTIFICATION OF PHASES)

The identification of the phase composition of an unknown sample by XRPD is usually based on the visual or computer-assisted comparison of a portion of its X-ray powder pattern to the experimental or calculated pattern of a reference material. Ideally, these reference patterns are collected on well-characterized single-phase specimens. This approach makes it possible in most cases to identify a crystalline substance by its 2θ-diffraction angles or d-spacings and by its relative intensities. The computer-aided comparison of the diffraction pattern of the unknown sample to the comparison data can be based on either a more or less extended 2θ-range of the whole diffraction pattern or a set of reduced data derived from the pattern. For example, the list of d-spacings and normalized intensities, I_{norm}, a so-called (d, I_{norm}) list extracted from the pattern, is the crystallographic fingerprint of the material and can be compared to (d, I_{norm}) lists of single-phase samples compiled in databases.

For most organic crystals, when using Cu Kα radiation, it is appropriate to record the diffraction pattern in a 2θ-range from as near 0° as possible to at least 40°. The agreement in the 2θ-diffraction angles between specimen and reference is at least 0.1° for the same crystal form, while relative intensities between specimen and reference may vary considerably due to preferred orientation effects. For other types of samples (e.g., inorganic salts), it may be necessary to extend the 2θ region scanned to well beyond 40°. It is generally sufficient to scan past the 10 strongest reflections identified in single-phase X-ray powder diffraction database files.

It is sometimes difficult or even impossible to identify phases in the following cases:

- noncrystallized or amorphous substances,
- the presence of the components to be identified in low mass fraction of the analyte amounts (less than 10% *m/m*, except in favorable cases),
- pronounced preferred orientation effects,
- the phase has not been filed in the database used,
- formation of solid solutions,

- the presence of disordered structures that alter the unit cell,
- the specimen comprises too many phases,
- the presence of lattice deformations,
- structural similarity of different phases.

QUANTITATIVE PHASE ANALYSIS

If the sample under investigation is a mixture of two or more known phases, of which not more than one is amorphous, the percentage (by volume or by mass) of each crystalline phase and of the amorphous phase can in many cases be determined. Quantitative phase analysis can be based on the integrated intensities, on the peak heights of several individual diffraction lines,[8] or on the full pattern. These integrated intensities, peak heights, or full-pattern data points are compared to the corresponding values of reference materials. These reference materials must be single phase or a mixture of known phases. The difficulties encountered during quantitative analysis are due to specimen preparation (the accuracy and precision of the results require, in particular, homogeneity of all phases and a suitable particle size distribution in each phase) and to matrix effects.

MATRIX EFFECTS

Matrix effects corrections consist of eliminating or estimating the absorption phenomenon, except in the case of mixtures of polymorphic samples in which all phases have the same absorption coefficients. However, it should be noted that in the case of organic systems, such effects are rather limited; hence, corrections can in many such cases be neglected.

[8] If the crystal structures of all components are known, the Rietveld method can be used to quantify them with good accuracy. If the crystal structures of the components are not known, the Pawley method or the partial least-squares (PLS) method can be used.

POLYMORPHIC SAMPLES

For a sample composed of two polymorphic phases *a* and *b*, the following relationship can be written for the concentration C_a of phase *a*:

$$C_a = \frac{1}{1 + K(I_b / I_a)}$$

The concentration is derived by measuring the intensity ratio between the two phases, knowing the value of the constant K. K is the ratio of the absolute intensities of the two pure polymorphic phases I_{oa} / I_{ob}. Its value can be determined by measuring standard samples.

METHODS USING A STANDARD

The most commonly used methods for quantitative analysis are

- the external standard method,
- the internal standard method, and
- the spiking method (also often called the standard addition method).

The external standard method is the most general method and consists of comparing the X-ray diffraction pattern of the mixture, or the respective line intensities, with those measured in a reference mixture or with the theoretical intensities of a structural model, if it is fully known.

To limit errors due to matrix effects, an internal reference material can be used that has a crystallite size and X-ray absorption coefficient comparable to those of the components of the sample and that has a diffraction pattern that does not overlap at all that of the sample to be analyzed. A known quantity of this reference material is added to the sample to be analyzed and to each of the reference mixtures. Under these conditions, a linear relationship between line intensity

and concentration exists. This application, called the internal standard method, requires precise measurement of diffraction intensities.

In the spiking method (or standard addition method), some of the pure phase *a* is added to the mixture containing the unknown concentration of *a*. Multiple additions are made to prepare an intensity-versus-concentration plot in which the negative *x*-intercept is the concentration of the phase *a* in the original sample.

ESTIMATE OF THE AMORPHOUS AND CRYSTALLINE FRACTIONS

In a mixture of crystalline and amorphous phases, the crystalline and amorphous fractions can be estimated in several ways. The choice of the method used depends on the nature of the sample:

- If the sample consists of crystalline fractions and an amorphous fraction of different chemical compositions, the amounts of each of the individual crystalline phases may be estimated using appropriate standard substances, as described above. The amorphous fraction is then deduced indirectly by subtraction.
- If the sample consists of one amorphous and one crystalline fraction, either as a 1-phase or a 2-phase mixture, with the same elemental composition, the amount of the crystalline phase (the "degree of crystallinity") can be estimated by measuring three areas of the diffractogram:

  A = total area of the peaks arising from diffraction from the crystalline fraction of the sample,

  B = total area below area A,

  C = background area (due to air scattering, fluorescence, equipment, etc).

When these areas have been measured, the degree of crystallinity can be roughly estimated as:

$$\% \text{ crystallinity} = 100A/(A + B - C)$$

It is noteworthy that this method does not yield an absolute degree of crystallinity values and hence is generally used for comparative purposes only. More sophisticated methods are also available, such as the Ruland method.

OBTAINING STRUCTURAL INFORMATION FROM AN XRPD PATTERN

XRPD has been an important standard tool for many decades for the identification and characterization of crystalline materials. The recent development of XRPD methods also allows some relevant structural information to be extracted from accurate XRPD data, as briefly described below.

Determination of Lattice Parameters

In an XRPD, each line can be associated with a *d*-spacing and the Miller indices {*hkl*} of the corresponding family or families of planes if the unit cell of the lattice is known (crystal system, Bravais lattice, approximate lattice parameters). The *d*-spacings measured from the diffractogram are related to the lattice parameters by geometric relations involving the Miller indices of the planes considered. If the material studied consists of crystalline phases for which the corresponding lattice parameters are approximately known, the lattice parameters can be refined by a least-squares method, using the whole powder pattern or a list of indexed *d*-spacings.

If the material studied consists of an unknown crystalline phase, the determination of the lattice parameters requires ab initio indexing of the XRPD pattern. This results in Mil-

ler indices being attributed to each line of the observed diffractogram. It can be accomplished by comparison with a reference pattern or by automatic indexing programs. Whether the mathematical solution found by an automatic indexing program is the true crystallographic unit cell or only a "pseudocell" depends on the completeness and uncertainty of the experimental data and on the size and symmetry of the unit cell.

Structure Solution

In general, the determination of crystal structures is performed from X-ray diffraction data obtained using single crystals. However, when substances cannot be prepared in the appropriate pure crystallographic form, this conventional approach cannot be employed. Recent developments based on high-resolution X-ray diffraction techniques using powders have led to significant progress in crystal structure determination. Crystal structures can sometimes be determined from sufficiently well-resolved powder diffraction data by applying trial and error, Patterson methods, and/or direct methods. However, crystal structure analysis of organic crystals is a challenging task, because the lattice parameters are comparatively large, the symmetry is low, and the scattering properties are normally very low. For any given crystalline form of a substance, the knowledge of the crystal structure allows for calculating the corresponding XRPD pattern, thereby providing a preferred orientation-free reference XRPD pattern, which can then be used for batch comparisons.

Refinement of Crystal Structures

Refinement of crystal structures consists of minimizing the difference between the intensities of the experimental diffraction pattern of a crystalline substance and the intensities calculated from a structural model sufficiently close to the true structure. The minimization is carried out using a least-squares method (or other procedure) to refine the structural parameters of the model (unit cell dimensions, atom coordinates, site occupancies) and the atomic displacement parameters until a satisfactory agreement between calculated and observed intensities is obtained. This application requires accurate diffraction data (intensity and position), containing sufficient information to estimate the structural parameters concerned. Structure refinement is most often carried out by methods of the Rietveld type, but the integrated-intensity method can also be applied.

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).

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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.

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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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Microbial Testing for Orally Inhaled and Nasal Drug Products

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ABSTRACT The Aerosols Expert Committee proposes adding the following text to a future version of General Chapter ⟨601⟩ *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* to provide microbiological sampling methods and accompanying specifications for orally inhaled and nasal drug products (OINDP) that are not required to be sterile. Note that *Aqueous OINDP* (e.g., single-dose inhalation solutions or aqueous solutions for inhalation) are required to be sterile, and these products are not addressed here except that certain general principles concerning aseptic sampling, as described below, may also apply to sterile OINDP during opening and testing of finished products. These procedures have been developed with the assistance of USP's Project Team 7.

MICROBIAL TESTING FOR ORALLY INHALED AND NASAL DRUG PRODUCTS (OINDP)

OINDP microbial testing involves Microbial Enumeration Tests (e.g., to determine the number of colony-forming units, CFU, per unit of measure) and Tests for Specified Microorganisms (e.g., Absence of *Staphylococcus aureus*). Each type of OINDP has its own challenges, and therefore test recommendations are divided into two groups: (1) *Low-Content OINDP* and (2) *High-Content OINDP.* These two groups are defined based on the target fill of the *primary container unit* (hereafter referred to as *unit*), which is the immediate enclosure containing the formulation in the finished product (e.g., canister, foil blister, capsule, vial, spray container, etc.).

Low-Content OINDP are those with a target fill of no more than (NMT) 100 mg of powder or 1 mL of liquid formulation per unit. Examples are premetered dry powder inhalers (DPIs) and single-dose nasal sprays.

High-Content OINDP are multidose drug products with a target fill of more than 100 mg of powder or more than 1 mL of liquid formulation per unit. Examples are pressurized metered-dose inhalers (MDIs) for oral inhalation and intranasal delivery, reservoir DPIs, and multidose nasal sprays.

Following sampling using one or more of the methods described below, testing should be performed in accord with General Chapter ⟨61⟩ and products should comply with the *Acceptance Criteria (Table 1)*. Testing may be performed on the unpackaged bulk or the finished product according to *Microbial Limit Tests* ⟨61⟩. However, if testing is performed on bulk alone, then the process leading from the bulk to the finished product must be validated to confirm its ability to prevent microbial contamination. Testing of the finished product must be performed if that process is not validated.

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Table 1. Acceptance Criteria for Microbiological Quality of Orally Inhaled and Nasal Drug Products*

Dosage Form and Type of Testing	Total Aerobic Microbial Count†	Total Combined Yeasts and Molds Count	Specified Organisms
Bulk loose powder or bulk filled capsules for low-content OINDP for pulmonary delivery	NMT 100 CFU/g	NMT 10 CFU/g	Absence (per 1 g) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria
Bulk formulation for low-content nasal products	NMT 100 CFU/g or mL	NMT 10 CFU/g or mL	Absence (per 1 g or mL) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria
Finished product–low-content OINDP for pulmonary delivery	NMT 10 CFU/unit§	NMT 10 CFU/unit	Absence (per 10 units§) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria
Finished product–low-content OINDP for nasal delivery	NMT 10 CFU/unit	NMT 10 CFU/unit	Absence (per 10 units§) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria
Finished product–inhalation and nasal products in pressurized MDIs and reservoir DPIs	NMT 100 CFU/unit	NMT 10 CFU/unit	Absence (per 1 unit§) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria
Finished product–multidose nasal sprays	NMT 100 CFU/g or mL	NMT 10 CFU/g or mL	Absence (per 1 g or mL) of *Staphylococcus aureus, Pseudomonas aeruginosa,* and bile-tolerant Gram-negative bacteria

* OINDP not required to be sterile.
† The exact limits provided in this table may not be acceptable to FDA for all products.
§ The term *unit* refers to the primary container unit, described above. When microbial counts are expressed in CFU/g, *gram* refers to the formulation—including active ingredient(s), propellant(s), excipient(s), co-solvent(s), surfactant(s), etc.—together with soluble capsules when used. As explained in USP chapter ⟨61⟩, an ''error factor'' of 2 may be applied to the stated acceptance criteria, meaning that an experimentally determined total count of up to twice the stated value can be considered acceptable.

SAMPLE SIZE

Select a sample size as follows:
Finished Product Low- and High-Content OINDP

Sample ten (10) drug product containers or units representative of the batch for each microbiological test. For batch sizes smaller than 200 units (e.g., batches used in clinical trials), sample size may be reduced to 1% of the units or 1 unit, respectively, whichever is greater. The contents of individual containers may be pooled for testing. In cases where the primary product container is demonstrated to be soluble in the microbiological testing media (e.g., soluble capsules), the test may be done on the unopened filled capsules to minimize potential for microbial contamination during opening. When testing filled capsules, include the weight of both the capsules and formulation contained therein in the weight of the material and the calculation of CFU/g.

Bulk Testing for Low-Content OINDP

Bulk-lot testing may be preferable for Low-Content OINDP in lieu of finished-product testing to allow for larger sample sizes representative of the batch without unduly increasing the risk of inadvertent microbial contamination. Bulk testing can be performed on the bulk powder or liquid formulation just prior to filling or on bulk filled capsules if the capsule is soluble in the microbiological media. If bulk testing is performed in lieu of finished-product testing, then manufacturing processes subsequent to bulk sampling (e.g., filling and packaging) must be validated in accordance with cGMP for their ability to prevent microbial contamination. It is further recommended that a program of periodic, but intermittent, testing of the finished product be implemented (e.g., skip-lot testing), the frequency of which is based on the product's manufacturing and microbiological history. Sample at least 10 g or 10 mL of bulk material for microbial enumeration tests and 1 g or 1 mL of bulk material for the

tests for specified microorganisms. When testing filled capsules, include the weight of both the capsules and formulation contained therein in the weight of the material and the calculation of CFU/g. For small batch sizes (i.e., less than 1000 g or 1000 mL), the recommended sample size is 1% of the batch for enumeration tests and 0.1% of the batch for tests for specified microorganisms.

SAMPLING PROCEDURES FOR HIGH-CONTENT OINDP

Select a sampling procedure from the list below. In all cases, employ aseptic techniques whenever necessary to avoid contamination of samples.

Propellant-Based Pressurized MDIs

1. Automatic Actuation Method

The contents of MDI containers may be collected by automatically actuating each MDI and collecting the delivered formulation on a suitable sterile filter.

2. Room-Temperature Method

Disinfect the outside of the test containers with an appropriate disinfectant and allow the containers to dry in an aseptic environment.

Using a needle apparatus or similar device, empty the MDI into a sterile vessel. If it has been demonstrated during Preparatory Testing (⟨USP 61⟩) that the propellant does not inhibit the growth of microorganisms, the contents of the sterile vessel may be added directly to the liquid media or buffer. Otherwise, allow the propellant to evaporate from the vessel by leaving the vessel at room temperature for several minutes and "pouring off" the gaseous propellant by tilting the vessel slightly, or by allowing a slow stream of microbiologically inert sterile gas to pass over the surface. For some less volatile propellants, such as CFC 11–CFC 12 combinations, heating the vessel slightly (to temperatures $\leq$45 °C) may be used to assist with evaporation. After evaporation, add the liquid media or buffer and mix the contents to prepare for testing.

If a needle apparatus is available and is thin and strong enough to puncture the container and allow slow removal of the contents, direct expulsion into the broth media or buffer may be feasible. In this case, the contents may be expelled into and mixed with the aqueous medium. Layering of the propellant and aqueous medium may occur, in which case a longer time period and slight heating (not to exceed 45 °C) may be required for propellant evaporation.

3. Chilling Method

Disinfect the outside of the test containers with an appropriate disinfectant and allow the containers to dry in an aseptic environment. Place the disinfected MDI containers in dry ice or dry ice slurry (ensure the microbial quality of the dry ice and slurry-forming liquid) or cryofreezer for the period required to liquefy the contents. Aseptically open the MDI containers using an appropriate tool.

For CFC-based products, pour the contents of containers into sterile vessels. Allow the propellant to escape, and combine residues with an appropriate diluent for the drug product. Other drug-specific procedures may also be employed.

For HFA-based products, pour the contents of the containers into sterile vessels partially immersed in larger vessels containing dry ice. Drive off the propellant, for example by allowing a slow stream of sterile, filtered, oil-free compressed air to evaporate the material to dryness. Combine residues with an appropriate diluent for the drug product.

An alternative procedure when testing the entire contents of a previously chilled container is to pour the contents of the opened container onto a sterile membrane filtration unit, allow the propellant to escape, then rinse with an appropriate amount of sterile diluent.

Reservoir DPIs

If the reservoir DPI has a fill plug, appropriate procedures used to sample a nonsterile drug product container should be employed.

Multidose Nasal Sprays

The container usually has a cap that is screwed on, crimped on, or forms a "snap-fit." The container can be opened by unscrewing the cap, cutting the seal, or using a decrimping tool, taking care to avoid microbial contamination during the process.

Specification Justification

The recommended acceptance criteria outlined in *Table 1* are based on Project Team 7's assessment of clinical relevance, test method sensitivity and variability, process capability for currently marketed products, and a desire to promote harmonization with the limits proposed in the *European Pharmacopoeia*.

The potential clinical impact on immunocompromised patients was assessed by considering the scientific data developed by the Centers for Disease Control (CDC) and published in the 2001 draft *Guideline for Environmental Infection Control in Health-Care Facilities.* That CDC draft guidance advises an upper limit of 15 CFU/m^3 of environmental air for gross colony counts of fungal organisms and 0.1 CFU/m^3 of environmental air for *A. fumigatus* and other potentially opportunistic fungi in heavily filtered air in critical-care areas. The CDC article further states that there is a lack of correlation between fungal species in the environment and clinical specimens. The upper limit of 15 CFU/m^3 equates to an exposure of 120 CFU/24 h, which is greater than the potential exposure from an MDI or DPI product with a limit of NMT 100 CFU/g or NMT 100 CFU/unit. However, FDA cautions that microbial limits developed for ambient air may not be appropriate for orally inhaled drug products. This uncertainty is due to the question of what specific data were used to support the safety of those environmental limits and whether such data can be extrapo-

lated to the setting of an orally inhaled drug product. These products are intended, by both design and by method of use, specifically to reach deep into the lung, potentially in patients with pre-existing lung disease.

The total aerobic microbial count specification of 100 CFU/g also takes into account the test method sensitivity and variability. USP Chapter ⟨61⟩ *Microbial Limit Tests* acknowledges that it provides an "estimation" of viable microorganisms in pharmaceutical items. Furthermore USP General Chapter *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩ under the section *Estimating the Number of Colony-Forming Units* states "as the number decreases, random error plays an increasing role in the estimate [of total aerobic microbial count]." The USP Chapter ⟨61⟩ test normally requires a 1:10 or 1:100 dilution that correlates to a limit of detection of <10 CFU/g and <100 CFU/g, respectively. Thus a limit tighter than 100 CFU/g is not practical for all currently marketed MDI and DPI products.

The microbial quality of MDIs and DPIs is greatly influenced by nonsterile raw materials, components, and manufacturing environments (e.g., Class 10,000 or 100,000) used to produce these products. An industry survey indicates that although producers implement manufacturing controls to minimize microbial contamination, the air classification of the manufacturing areas and microbiology testing facilities and procedures may account for low-level microbial contamination. Because many companies do not manufacture sterile products at the same facilities as MDI and DPI products, costly microbiology laboratory upgrades are not justified for nonsterile inhalation products. However, companies are expected to monitor and investigate microbial results that fall outside expected trends for the product.

The collective evaluations of test method sensitivity/variability and process capability indicate that the proposed limits are appropriate for nonsterile inhalation products. However, cGMPs dictate that appropriate controls to minimize microbial contamination should be incorporated into the manufacture of all nonsterile OINDPs.

COMMENTS

Comments regarding these proposals are solicited from all interested parties. These should be sent to arrive on or before October 7, 2005, and should be addressed to Kahkashan Zaidi, Ph.D., Drug Standards Division, USP, 12601 Twinbrook Parkway, Rockville, MD, 20852-1790; e-mail: kxz@usp.org. Comments will be debated prior to the publication of a revised form of this text in the *In-Process Revision* section of *Pharmacopeial Forum*.

USP-International: Responses to Comments on *Stimuli* Article

United States Pharmacopeia Staff[*]

ABSTRACT In the September–October 2004 issue of *Pharmacopeial Forum—PF* 30(5)—USP published a *Stimuli* article titled "Development of a New Official Compendium, Separate from *USP–NF,* for Articles Not Legally Marketed in the U.S." (*1*). That *Stimuli* article specifically solicited public comment about the prospective launch of a new compendium, *USP-International,* and on 10 December 2004, USP also convened an invitational meeting regarding *USP-International*. The present *Stimuli* article summarizes and responds to all comments received following publication of the original article.

BACKGROUND

In the September–October 2004 issue of *Pharmacopeial Forum—PF* 30(5)—USP published a *Stimuli* article titled "Development of a New Official Compendium, Separate from *USP–NF,* for Articles Not Legally Marketed in the U.S." (*Stimuli* article) (*1*). The *Stimuli* article was published at the request of the Task Force on Public Health Program #1 ("Task Force"), which was formed by the USP Board of Trustees following a Council of Experts Executive Committee vote in July 2003 to include in *USP–NF* monographs for articles not legally marketed in the United States but available in international commerce. The purpose of the *Stimuli* article was to solicit input regarding how this Council of Experts Executive Committee vote might be implemented and to offer a proposal for effectuating the Committee's decision through publication of a separate compendium (referred to herein as *USP-International* or *USP-I*). On November 16, 2004, again at the request of the Task Force, Dr. Roger Williams issued a letter to members of the USP Convention and Executive Officers of Eligible Organizations, members of the Council of Experts and Expert Committees, and USP stakeholders requesting responses and feedback to the *Stimuli* article.

In addition to the publication of the *Stimuli* article and the solicitation of comments, an invitational meeting regarding *USP-International* was held on December 10, 2004, to meet directly with trade organizations and representatives of the government. Dr. Edwin T. Bransome, USP Past President and Chair of the Task Force led the meeting. The following representatives attended:

- Gordon Johnston, R.Ph., Vice President, Regulatory Affairs, Generic Pharmaceutical Association
- Janeen Kincaid, Corporate Compendial Liaison, Pfizer
- Thomas McGinnis, R.Ph., Chief Pharmacist, FDA Office of Policy
- Yana R. Mille, R.Ph., Director, Regulatory, Office of Pharmaceutical Sciences, FDA Center for Drug Evaluation and Research
- Sara Radcliffe, M.P.H., Managing Director, Scientific and Regulatory Affairs, Biotechnology Industry Organization
- Fred Razzaghi, Director of Technical Affairs, Consumer Healthcare Products Association
- Andreas Seiter, M.D., Global Pharmaceutical Industry Fellow, World Bank
- Alice E. Till, Ph.D., Vice President, Science Policy and Technical Affairs, PhRMA
- Richard Walling, R.Ph., M.H.A., Office of Global Health Affairs, Rear Admiral, Assistant Surgeon General, Director of the Office of the Americas and Middle East.

Invitations to the December 10, 2004, meeting also were extended to the International Federation of Pharmaceutical Manufacturers and Associations, the International Generic Pharmaceutical Alliance, and the Pan American Health Organization, although representatives of those organizations were unable to attend.

Along with the feedback provided during the December 10, 2004, meeting, written comments responding to the *Stimuli* article were received from many constituencies, including USP Convention members, Council of Experts members, pharmaceutical manufacturers, trade associations, and government representatives.

Seventy-one Convention and Council of Experts members responded to the call for comments for a response rate of approximately 5%. The majority of these respondents expressed support for the general approach proposed in the *Stimuli* article, noting USP's unique position as a recognized leader in national and international standards-setting, its perceived ability to implement such an effort, and the timeliness of the initiative. Several specifically noted the public health need for such a compendium, given the international nature of modern pharmaceutical research and manufacturing and the increasingly global distribution and use of pharmaceutical products. The respondent breakdown among

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Convention and Council of Experts members was as follows: 17 (24%) were Convention members; 12 (17%) were members of the Council of Experts (Expert Committee chairs); 40 (56%) were Expert Committee members; and two (2%) did not indicate their affiliation. Of the comments, 60 (85%) were supportive. Of the remaining responses, one (1%) indicated conditional support, and 10 (14%) did not indicate whether or not they supported the concept but provided comments.

Responses from 13 stakeholders also were received. Respondents included: the Center for Drug Evaluation and Research of the Food and Drug Administration, Consumer Healthcare Products Association, Eli Lilly & Company, Hoffmann–La Roche, Inc., Generic Pharmaceutical Association, J.B. Chemicals and Pharmaceuticals Limited, New Jersey Pharmaceutical Quality Control Association, Pfizer, Inc., Pharmaceutical Research and Manufacturers of America, Purdue Pharma, L.P., World Bank, World Health Organization (WHO), and Wyeth. The comments of the Center for Drug Evaluation and Research, the Consumer Healthcare Products Association, the Generic Pharmaceutical Association, WHO, and World Bank were supportive and offered constructive comments. The remainder of these stakeholder respondents generally voiced strong concerns about or disagreement with the concept of *USP-I*.

In the following summary, USP has organized the issues and concerns raised by respondents in both Convention/Council of Experts and stakeholder groups into major categories and has responded to each of these categories.

SUMMARY OF, AND RESPONSES TO, ISSUES RAISED BY COMMENTATORS

A. Resource Limitations and Constraints

Issues

The concern most frequently voiced by respondents was whether USP would have sufficient financial and other resources to undertake *USP-I* without detracting from or consuming resources necessary for the continued maintenance of *USP–NF*. In some cases, respondents noted the large number of missing or outdated monographs in *USP–NF* as evidence of the need to concentrate resources first on closing these gaps within *USP–NF*. One respondent noted the cessation of *USP-DI* activities and expressed hope that if *USP-International* were pursued, the same fate would not befall it.

Response

USP has no intention of diverting resources away from *USP–NF* to support *USP-I* or to allow *USP-I* in any way to detract from USP's ongoing commitment to maintain *USP–NF* as the official compendia of the United States of America produced through USP's standards-setting activities. Rather, it is the expectation that, over time, *USP-I* coupled with official USP Reference Standards could become self-sustaining just as *USP–NF* has been. However, USP fully recognizes the need for careful, comprehensive business planning to ensure that the development of *USP-I* can proceed in a financially responsible and feasible manner. USP also acknowledges that there are specific resource issues that need to be addressed, such as whether Council of Experts members have sufficient time and expertise to devote to *USP-I*; some of these are discussed further below, and others will be addressed as planning for the project continues.

USP also has no intention of lessening its efforts to obtain missing monographs for articles marketed in the U.S. or to update existing monographs. However, the primary barrier to resolving these issues is not a lack of resources on USP's part; rather, as discussed in the *Stimuli* article, it is more often reluctance on the part of pharmaceutical manufacturers to provide the necessary information. Given the voluntary nature of donation of the information required to develop and update monographs, it is unlikely that these issues can be resolved soon. Meanwhile, USP believes it can make a significant contribution to public health by developing standards for articles marketed outside the U.S. via *USP-International*. There is no expectation that resources for *USP-I* should result in an increase in prices for USP's current line of products and services.

B. USP's Ability to Develop Sound Monographs for Products Not Approved in the U.S.

Issues

Several respondents raised questions regarding whether USP would have the ability to develop high-quality monographs for drugs not approved in the U.S., given 1) the possibility that foreign manufacturers might also be reluctant to provide information; 2) the absence of competent regulatory authorities in some countries to provide review and oversight; and 3) the potential lack of scientific expertise and capabilities within USP and its Council of Experts that might be needed to develop the requisite information, especially in the absence of a competent regulatory authority. Some respondents were concerned generally about how USP could assure safety of products in international commerce. Others wondered—especially given the suggestion in the *Stimuli* article that *USP-I* could use WHO's model of providing classical procedures—whether *USP-International* might represent 4) a departure from USP's tradition of providing the most rigorous, science-based standards or an intent to create a "double standard" based on whether products were approved and marketed inside or outside of the U.S. Each of these sub-issues is specifically addressed below.

Response

1. Foreign Manufacturers' Willingness to Provide Monograph Information. USP recognizes that some foreign manufacturers may have the same reservations as some U.S. manufacturers do today with regard to furnishing monograph information. Having said that, USP believes there will

be a sufficient number of manufacturers who will be willing to provide information. Manufacturers of drugs in international commerce may see more value in the creation of a monograph than do U.S. manufacturers and so may be more likely to be willing to donate information and materials.

2. Lack of Regulatory Oversight; Safety Concerns. USP acknowledges that public monographs in *USP–NF* today rest on excellent work by highly committed pharmaceutical manufacturers as well as FDA. USP would point out that there now exist highly competent regulatory authorities in many '802 countries—countries that the U.S. government has evaluated as competent to receive unapproved drugs exported from the U.S. These authorities today allow market access in their respective countries based on review and acceptance of private or public standards to ensure the strength, quality, and purity of an article. This reflects the evolution of capability throughout the world, which arises in part as a result of the efforts of the International Conference on Harmonization (ICH). In this context, it seems appropriate for USP to begin its efforts on *USP-I* by working with competent regulatory agencies in other countries. With the experience gained in this initial phase, USP will be able to begin to develop expertise in obtaining and reviewing the kind of information needed to support a sound monograph.

USP also believes that it is important to not confuse clinical safety and efficacy of the drug substance and dosage form with some specific safety issues pertinent to a monograph. USP has no intention of engaging in the safety and efficacy evaluations that allow market access for a new drug or biologic. That evaluation is much better left to highly competent authorities such as those who participate actively in ICH.

There are, of course, issues of safety and/or efficacy for a public monograph that do not devolve directly on the drug substance, be it a drug or biologic. These relate primarily to limits for impurities, as reflected in the USP *Impurity* test (safety) and dosage form performance (safety and efficacy), as reflected in the USP *Performance* test. Again, for '802 countries, or some subset thereof, USP intends to work with a regulatory agency, specified by the Sponsor of the Request for Revision to *USP-I,* to gain needed information to support provisions of the monograph. For non-'802 countries, USP would have to develop capability to review impurity isolation, characterization, and qualification data to gain acceptance criteria for the *Impurity* test. For the acceptance criterion for the USP *Performance* test (e.g., dissolution *Q* value), USP would have to review bioavailability-bioequivalence (BA/BE) studies.

Finally, USP notes the approach of the European Department for the Quality of Medicines (EDQM) wherein an administrative unit of that organization, working with Member State regulators, reviews impurity data to reach a community-wide decision on impurity limits and other safety issues for a drug substance.

3. Expertise of Council of Experts and Expert Committees. Although some of the areas identified above are of course new areas for USP, they are not beyond the knowledge base and capability of its Council of Experts and its Expert Committees. The Council of Experts Executive Committee has already begun to consider how it might formulate guidance for the development of *USP-I* monographs. Certainly, there would be one set of criteria for '802 countries with established and credible regulatory authorities, but the creation of criteria for countries with reduced regulatory resources would be more complex. Although tackling these issues may be challenging, it would also ultimately strengthen the scientific knowledge of the Council of Experts and Expert Committees and allow USP to become more self-reliant. The development of *USP-International* may also provide USP with opportunities to bring additional distinguished scientists from around the world into the Council of Experts and Expert Committees, further strengthening and supplementing the already considerable scientific capabilities within these bodies.

4. Use of Less Rigorous Standards for USP-I Monographs. USP does not intend to lower its quality standards in developing *USP-I.* In fact, as noted in the *Stimuli* article, the monographs in *USP-I* may be more relevant and science-based initially than the monographs in *USP–NF* because of the challenges of updating current monographs. USP also does not intend to create different monographs for the same material. However, this does not mean that the standards for articles under the same name are identical. The work of ICH as well as many other factors has resulted in what USP now terms the *flexible monograph.* This approach was developed with careful input from knowledgeable representatives of many U.S. manufacturers and acknowledges that tests within a monograph may be associated with different procedures and acceptance criteria. This is already an established position in *USP–NF,* where different dosage forms may require different Performance test procedures and acceptance criteria (e.g., for dissolution, the *Q* value). For the ingredient Impurity test, USP acknowledges the outcome of the ICH approach may require different Impurity test procedures and acceptance criteria for impurities arising from different routes of synthesis. This too is already an established position in *USP–NF.*[1] USP generally supports the goals of the Pharmacopeial Discussion Group (PDG) harmonization that speak to the best, most relevant compendial standards for all articles in commerce.

USP will always maintain its commitment to providing the most modern, relevant, and science-based monograph. However, within *USP-International,* it is possible that less demanding tests, including WHO screening/basic tests, could be placed in the informational section of monographs. Such tests have significant value in ensuring basic drug safety and quality in areas with only very rudimentary testing equipment and thus serve a critical public health need in

[1] For a more detailed discussion, please see the *USP Guideline for Submitting Requests for Revision to* USP–NF at www.usp.org/USPNF/submitMonograph/subGuide.html

underdeveloped and developing countries. Again, these are issues that can be further considered and refined by USP and its Council of Experts as development of *USP-I* progresses.

C. Intellectual Property

Issue

Some commentators from the pharmaceutical industry expressed concern that innovators' U.S. intellectual property rights might be compromised or jeopardized by USP's publication of monographs for articles not legally marketed in the U.S. In these commentators' views, *USP-I* could be used to circumvent the existing *USP–NF* monograph development process or allow generic manufacturers to prematurely gain access to monograph information.

Response

To some extent these comments reflect a larger disagreement between certain innovators and USP regarding the appropriate timing of the publication of a monograph for a product protected by a U.S. patent. USP has always believed that a public monograph (relating to quality) should accompany FDA-approved product labeling (relating to safety and efficacy) at the time of New Drug Application/Biologic License Application (NDA/BLA) approval. With this approach, practitioners, patients, and purchasers may view the triad of information needed for informed decision-making. The need was envisioned in the Federal Food, Drug, and Cosmetic Act (FDCA), which states that a firm may claim that an article is not "USP" or not "NF" if it differs from the standards of strength, quality, or purity established for the article in *USP* and if the difference is stated in the firm's product label. These statements are clearly separate and distinct from those portions of the FDCA that relate to generic substitution. USP also believes that an official Reference Standard allows FDA and other enforcing bodies to monitor the integrity of a manufacturer's manufacturing processes. Although candidate material for a product may come from the manufacturer, the subsequent work in USP, FDA, and other collaborating laboratories becomes a way to confirm, check, monitor over time, and—ultimately—endorse that manufacturer's manufacturing operations. In today's environment more than ever, the independent character of these processes is critical to the public health and in maintaining public trust.

Nevertheless, USP emphasizes that *USP-International* will provide monographs based on voluntary submission of information by a Sponsor in a Request for Revision, just as now occurs in Requests for Revision to *USP–NF*. Thus transmission of trade secret information, such as validated analytical procedures, as always, will continue to be the choice and the responsibility of the Sponsor.

USP acknowledges that intellectual property protection is an important concern for innovators and one that is heightened by the fact that other countries do not necessarily follow the intellectual property approaches of the U.S. However, it is not within USP's province or mission to ensure the protection of manufacturers' intellectual property or to promote or advocate certain intellectual property laws and approaches over others. These issues will continue to be determined by the respective governments of individual countries, working within the broader context of the World Trade Organization and influenced by other associations and organizations whose mission it is to advance these issues. Those governments will also continue to determine issues of market access within their individual countries.

Certainly, USP will continue to respect the laws—including intellectual property laws—of the various nations and regions in which it operates. USP has always endeavored to abide by such laws. However, USP's mission and vision, as shaped by its charter and Board of Trustees, is to assure the quality of drugs already in commerce throughout the world. Publication of *USP-I* fits squarely within this mission and vision and should not be derailed by intellectual property concerns that are beyond the purview or control of USP.

D. Counterfeit and Substandard Drugs

Issue

Somewhat related to the intellectual property issues discussed above are questions raised by some respondents about whether USP's publication of monographs for articles not approved in the U.S. might be perceived as legitimizing or validating such articles in this country or might otherwise facilitate the illegal entry of such articles into the U.S.

Response

As noted above and stated clearly in the *Stimuli* article, *USP-International* is not intended to be a mechanism for market access in the U.S. That responsibility lies with the U.S. government through its work with FDA and other agencies. Indeed, as outlined in the *Stimuli* article, *USP-I* should be seen in this regard as a means to keep certain articles out of the U.S. market by appropriate surveillance testing.

With regard to substandard products, USP maintains, as noted in the *Stimuli* article, that monographs in a separate compendium might in fact assist foreign regulatory bodies, customs officials, purchasing agents, and other groups and individuals in understanding how to test articles legitimately marketed within a country or in international commerce. USP believes it is in the interest of public health and its stakeholders, as well as USP, to ensure that articles in international and national commerce are of acceptable quality. Substandard products, even when made by well-intentioned manufacturers, do nothing to serve legal and legitimate interests, detracting as they do from public trust in acceptably manufactured articles. The absence of public procedures to test counterfeit medicines raises an even larger challenge for affected countries. Although USP acknowledges that *USP-I* monographs might not in every case allow officials to distinguish between acceptable and substandard products, these limitations should not deter USP from doing what it can to assist in the effort to combat the introduction of sub-

standard drugs globally. As noted above, even basic tests can be of value in the battle against substandard and counterfeit drugs. And over time, USP and its Council of Experts can continue to consider how additional tests and information might be used to detect more sophisticated counterfeit drugs. Again, through directives of this and prior USP Boards of Trustees and Conventions, USP is charged with using its capabilities to help assure the good quality of safe and effective products not only in the U.S. marketplace but throughout the world, and *USP–International* represents an important step in fulfilling this charge.

E. Acceptance by the International Community; Coordination with Existing International Efforts

Issues

Some commentators raised issues regarding USP's outreach to the international health community to validate the need for and acceptance of the new publication. They also questioned whether USP should instead be focusing on supporting WHO's *International Pharmacopoeia* and/or international harmonization efforts. Each of these issues is addressed below.

Response

1. Acceptance of USP-I by the International Community. Based on its outreach to and discussions with constituents in other countries, including regulatory authorities, manufacturers, and practitioners, USP believes that much of the international health community will welcome the standards and information made available in *USP-International*. More generally, USP firmly believes that the proposed separate compendium will amplify USP's international public health opportunities and contributions, not only with WHO and manufacturers but also with professional associations such as the World Medical Association, FIP, and the International Council of Nurses—practitioner-based constituencies operating globally. In building and expanding its scientific capabilities to support *USP-International,* USP will pursue a multilateral approach, working with responsible and sophisticated pharmaceutical scientists throughout the world. In this regard, the effort should be viewed in the finest traditions of international assistance.

2. Support for WHO's International Pharmacopoeia. USP is proud of its record of supporting WHO's work (one indication of which is the four-drug tuberculosis monograph now included in *USP–NF,* which arose as a result of a request from WHO staff). As indicated in the *Stimuli* article, the development of *USP-International* would allow USP to support WHO's activities to an even greater extent. Generally, it is anticipated that *USP-International* would focus on monographs for legally marketed medicines in non-U.S. countries other than medicines on WHO's Essential Medicines List (EML), and WHO would continue to provide monographs for medicines on the EML. However, there are special cases in which USP could provide assistance even for EML medicines. For example, USP's Global Assistance Initiatives (GAI) staff, working under a USAID grant and at the request of WHO and the United Nations International Children's Emergency Fund (UNICEF), developed monographs for Zinc Sulfate Tablets and Zinc Sulfate Oral Solution [*PF* 31(1) and 31(2), respectively]. Pending USAID approval, USP may also develop reference standards for these zinc products. GAI also has initiated activity to develop a monograph on nevirapine oral suspension for pediatric use, and recently WHO has asked USP to develop monographs for certain first-line antituberculosis drugs. There are other opportunities for synergy and collaboration as well. In some cases, it may be appropriate for monograph submissions to *USP-International,* which will be reviewed and considered by USP's Council of Experts, to also be evaluated through the WHO consultative process. Based on the two "consultations"—one in the USP Council of Experts and one in WHO—the monographs could appear both in *USP-International* and in the WHO *International Pharmacopoeia,* perhaps with certain justifiable differences. As mentioned, USP has previously engaged in this kind of joint effort with WHO in developing a four-drug tuberculosis dosage form monograph, working with WHO staff and consultants.[2]

3. International Harmonization Efforts. USP continues to support international harmonization efforts and expects that development of *USP-International* would have little, if any, impact on its current harmonization efforts through PDG. PDG focuses on harmonization of excipient monographs and General Chapters. Any excipient monographs and General Chapters that have been harmonized and are applicable to *USP-International* could appear in both compendia. USP recognizes the need for additional resources to allow USP to continue to develop monographs for *USP–NF* and the new compendia as well as for its PDG efforts and is prepared to make these resources available. At its Convention 2005, USP adopted Resolution 7, which calls on USP "to continue its efforts to harmonize compendial standards with the Pharmacopeial Discussion Group (PDG) amd other pharmacopeias."

F. Additional Implementation Issues and Considerations

Issues and Responses

Respondents submitted miscellaneous comments and questions on a variety of issues related to the implementation of *USP-International.* Some of these related to the naming of the *USP-I* publication, and others voiced concerns regarding potential confusion with *USP–NF.* Specifically, some respondents urged USP to refine the publication's name to clearly identify the market in which it is intended to be used and to be clear regarding the scope that it intends

[2] Indeed, should *USP-International* come into being, perhaps a first task would be to transfer this and the zinc products monographs out of *USP–NF* and into *USP-International,* given that these products are not legally marketed in the U.S.

to cover (e.g., drugs, biologics, etc.). USP agrees that these issues require further consideration and will be examined in the business-planning process.

There were also comments regarding the appropriate placement of certain monographs, and a few commentators were not convinced that a separate compendium was the optimal way to publish monographs for articles not approved in the U.S. USP continues to believe, as does FDA, that a separate compendium is the clearest way to distinguish between *USP–NF* and *USP-International.* However, USP acknowledges the need for further discussion of issues regarding where to place individual monographs and intends to more fully evaluate these issues.

Some respondents questioned the use of the *Pharmacopeial Forum* (*PF*) to solicit comments on *USP-International* monographs, again wondering about the possibility of confusion between the compendia. Others suggested that the use of *PF* for this purpose was appropriate but advocated clearly delineating a separate section within *PF* for *USP-I* monographs. USP believes this is a useful comment for further discussion. One way to handle these comments would be to demarcate a separate section of *PF.*

At times, respondents requested that USP provide more in-depth justification for *USP-I* monographs. USP believes that the availability of science-based, relevant monographs for therapeutic articles moving in international and national commerce speaks for itself, given that this is USP's primary activity.

Respondents also raised a question about whether monographs in *USP-I* would solve the backlog of monographs in *USP–NF.* The answer to this question is negative, given that there is no direct relationship between monographs in *USP–NF* and *USP-I.*

There were miscellaneous specific science-related issues raised by individual commentators, such as nomenclature, compounding, the availability of reference standards, and the treatment of botanicals and herbs. Although responding to each of these requires a level of detail not appropriate for this summary, USP appreciates these comments and agrees that these issues warrant further consideration and discussion as the project evolves.[3]

Finally, a few respondents raised issues of USP's governance documents and structure and whether these would allow pursuit of the *USP-I* initiative. Again, it is not appropriate to respond to these in detail here, but USP emphasizes that the development of *USP-International* falls squarely within USP's mission, which also allows USP's structure and membership to evolve to facilitate and support this endeavor.

REFERENCES

1. Council of Experts Executive Committee, Ad Hoc Council of Experts Committee, and USP Staff. Development of a new official compendium, separate from *USP–NF,* for articles not legally marketed in the U.S. *Pharm Forum.* 2004;30(5):1877–1883.
2. Saper RB, Kales SN, Paquin, J., et al. Heavy metal content of Ayurvedic herbal medicine products. *JAMA.* 2004;292:2868–2873.

[3] With regard to botanicals and herbs (including traditional medicines), USP notes that these articles especially may benefit from up-to-date monographs in *USP-I,* given the frequent absence of strong regulatory oversight (as in the U.S.). For example, recent literature articles document the presence of heavy metals in Chinese Traditional and Ayurvedic medicines; this is an example of a case in which harm might arise but could be alleviated by a modern monograph using the inductively coupled plasma analytic technique (*2*).

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
2005 USP DICTIONARY SUPPLEMENT 2

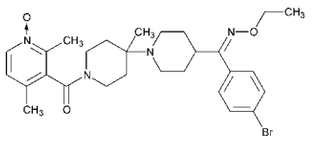
IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

Newly Approved United States Adopted Names (USAN), Released for Publication

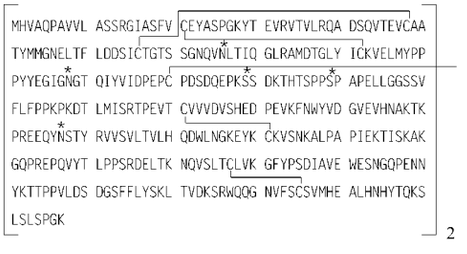
The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

Nomenclature

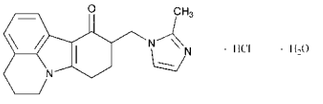
Ancriviroc [*2005*] (an″ kri vir′ ok). $C_{28}H_{37}BrN_4O_3$. 557.52. (1) [1,4′-Bipiperidine]-4-methanimine, α-(4-bromophenyl)-1′-[(2,4-dimethyl-1-oxido-3-pyridinyl)carbonyl]-*N*-ethoxy-4′-methyl-, (α*Z*)-; (2) 4-[(*Z*)-(4-Bromophenyl)(ethoxyimino)-methyl]-1′-[(2,4-dimethyl-1-oxidopyridin-3-yl)carbonyl]-4′-methyl[1,4′-bipiperidinyl].*CAS-370893-06-4*. INN. *Antiviral; treatment of autoimmune conditions* (*CCR5 antagonist*). (Schering-Plough Research) ✧*SCH351125*



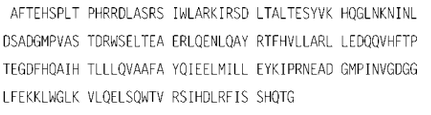
Belatacept [*2005*] (bel a ta′ sept). $C_{3508}H_{5440}N_{922}O_{1096}S_{32}$. 91,500 daltons. (1) CTLA-4 (antigen) [29-tyrosine,104-glutamic acid] (human extracellular domain-containing fragment) fusion protein with immunoglobulin G1 (human monoclonal Fc domain-containing fragment), bimol. (120→120′)-disulfide; (2) [Tyr;S2;S9,Glu;S1;S0;S4,Gln;S1;S2;S5,-Ser;S1;S3;S0,Ser;S1;S3;S6,Ser;S1;S3;S9,Ser;S1;S4;S8](CTLA-4 (antigen)-[3-126]-peptide (human extracellular domain-containing fragment) fusion protein with immunoglobulin G1-[233 *C*-terminal residues of the heavy chain]-peptide (human monoclonal Fc domain-containing fragment)) bimolecular (120→120′)-disulfide. *CAS-706808-37-9*. *Prevention of allograft rejection in recipients of solid organ transplants; prevention of graft-vs.-host disease following bone marrow transplantation; treatment of autoimmune diseases and conditions such as rheumatoid arthritis and Type 1 diabetes.* (Bristol-Myers Squibb) ✧*BMS-224818*



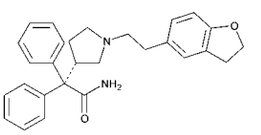
Cilansetron Hydrochloride [*2005*] (sil an se′ tron). $C_{20}H_{21}N_3O.HCl.H_2O$. 373.88. [Cilansetron is INN.] (1) 4*H*-Pyrido[3,2,1-jk] carbazol-11-(8*H*)-one, 5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl) methyl]-, monohydrochloride monohydrate (10*R*)-; (2) (10*R*)-5,6,9,10-Tetrahydro-10[(2-methylimidazol-1-yl)methyl)-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one monohydrochloride, monohydrate. *CAS-209859-87-0; CAS-120635-74-7* [cilansetron]. *Treatment of Irritable Bowel Syndrome* (*IBS*) *with diarrhea predominance.* (Solvay Pharmaceuticals B.V., Weesp, Netherlands) ✧*DU123265; KC-9946*



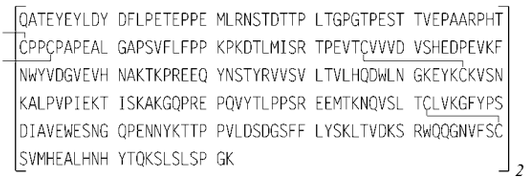
Dapiclermin [*2005*] (da′ pi kler min). $C_{945}H_{1482}N_{266}O_{278}S_3$. 21,114. (1) 2-185-Ciliary neurotrophic factor [17-alanine,63-arginine] (human isoform AXOKINE); (2) 2-185-[17-Alanine,63-arginine]ciliary neurotrophic factor-(2,185)-peptide (human isoform AXOKINE). *CAS-444069-80-1*. *Treatment of overweight and obesity.* Axokine (Regeneron)



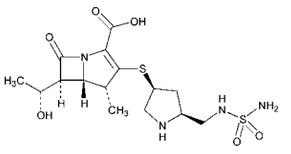
Darifenacin [*2005*] (dar ee fen′ a sin). $C_{28}H_{30}N_2O_2$. 426.60. (1) 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)-ethyl]-α,α-diphenyl-, (3*S*)-; (2) 2-[(3*S*)-1-[2-(2,3-Dihydrobenzofuran-5-yl)ethyl]pyrrolidin-3-yl]-2,2-diphenylacetamide. *CAS-133099–04-4*. *Treatment for an overactive bladder.* (Novartis) ✧*UK-88525*



Darunavir [*2005*] (dar ue′ na vir). $C_{27}H_{37}N_3O_7S$. 547.66. (1) [(1*S*,2*R*)-3-[[(4-Aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester; (2) Carbamic acid, [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester. *CAS-206361-99-1*. INN. *Treatment of HIV infection.* (Janssen); (Tibotec) ✧*TMC 114*

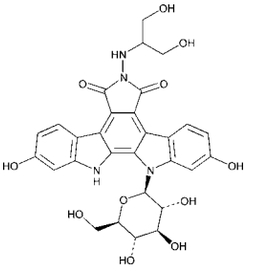


Doripenem [*2005*] (dore i pen′ em). $C_{15}H_{24}N_4O_6S_2$. 420.50. (1) 1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[[(3*S*,5*S*)-5-[[(aminosulfonyl)amino]methyl]-3-pyrrolidinyl]thio]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-, (4*R*,5*S*,6*S*)-; (2) (+)-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid. *CAS-148016-81-3*. INN. *Antibiotic.* (Shionogi, Japan) ✧*S-4661*

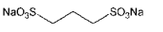


Ecallantide [*2005*] (ee kal′ lan tide). $C_{305}H_{442}N_{88}O_{91}S_8$. 7054. (1) Protein (synthetic human plasma kallikrein-inhibiting); (2) [Glu^{20},Ala^{21},Arg^{36},Ala^{38},His^{39},Pro^{40},Trp^{42}]tissue factor pathway inhibitor (human)-(20 79)-peptide (modified on reactive bond region Kunitz inhibitor 1 domain containing fragment); (3) Human plasma kallikrein-inhibitor (synthetic protein). *CAS-460738-38-9*. *Treatment of hereditary angioedema; reduction of blood loss during cardiothoracic surgery* (*plasma kallikrein inhibitor*). (Dyax) ✧*DX-88*

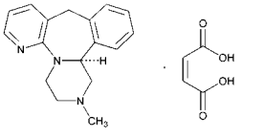
Edotecarin [*2005*] (ed oh tek′ ar in). $C_{29}H_{28}N_4O_{11}$. 608.55. (1) 5*H*-Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione,12-β-D-glucopyranosyl-12,13-dihydro-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-; (2) 12-β-D-Glucopyranosyl-2,10-dihydroxy-6-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-12,13-dihydro-6*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-dione. *CAS-174402-32-5*. INN. *Treatment of cancer.* (Pfizer) ✧*PF-804950*



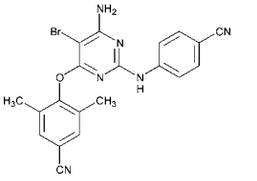
Eprodisate Disodium [*2005*] (e proe′ di sate). $C_3H_6Na_2O_6S_2$. 248.20. (1) 1,3-Propanedisulfonic acid, disodium salt; (2) Disodium propane-1,3-disulfonate. *CAS-36589-58-9*. *Treatment of secondary* (*AA*) *amyloidosis.* (Neurochem, Canada) ✧*NC-503*



Esmirtazapine Maleate [*2005*] (es mir taz′ a peen). $C_{17}H_{19}N_3.C_4H_4O_4$. 381.43. (1) Pyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14b*S*)-, (2*Z*)-butenedioate (1:1); (2) (+)-(14b*S*)-2-Methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine (2*Z*)-butenedioate. *CAS-680993-85-5*. *Treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of primary insomnia.* (Organon, Netherlands) ✧*Org 50081*

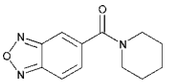


Etravirine [*2005*] (et′′ ra vir′ een). $C_{20}H_{15}BrN_6O$. 435.28. (1) Benzonitrile, 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl-; (2) 4-[[6-Amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl-benzonitrile.*CAS-269055-15-4*. INN. *Treatment of HIV infection.* (Janssen); (Tibotec) ✧*TMC 125*

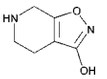


Nomenclature

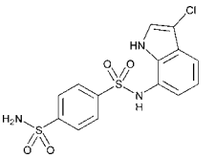
Farampator [*2005*] (far am′ pa tore). $C_{12}H_{13}N_3O_2$. 231.30. (1) Piperidine, 1-(2,1,3-benzoxadiazol-5-ylcarbonyl)-; (2) 1-(2,1,3-Benzoxadiazol-5-ylcarbonyl)piperidine. *CAS-211735-76-1*. INN. *Treatment of schizophrenia.* (N.V. Organon, Netherlands) *Org 24448; CX691*



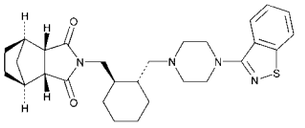
Gaboxadol [*2005*] (gab ox′ a dol). $C_6H_8N_2O_2$. 140.14. (1) Isoxazolo[5,4-*c*]pyridin-3(2*H*)-one, 4,5,6,7-tetrahydro-; (2) 4,5,6,7-Tetrahydroisoxazolo[5,4-*c*]pyridin-3(2*H*)-one. *CAS-64603-91-4*. INN. *Treatment of insomnia.* (H. Lundbeck, A/S) ✧*Lu 02-030; MK-0928*



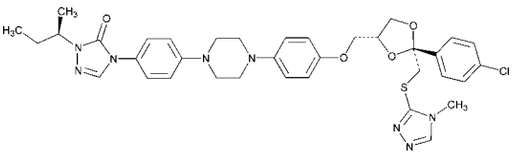
Indisulam [*2005*] (in″ di soo′ lam). $C_{14}H_{12}ClN_3O_4S_2$. 385.85. (1) *N*-(3-Chloro-1*H*-indol-7-yl)benzene-1,4-disulfonamide; (2) 1,4-Benzenedisulfonamide, *N*-(3-chloro-1*H*-indol-7-yl). *CAS-165668-41-7*. INN; BAN. *Antineoplastic.* (Eisai Medical Research) ✧*E7070*



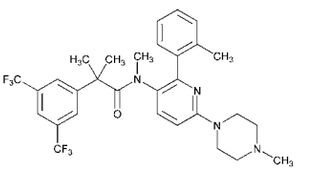
Lurasidone Hydrochloride [*2005*] (loo ras′ i done). $C_{28}H_{36}N_4O_2S.HCl$. 529.14. [Lurasidone is INN.] (1) 4,7-Methano-1*H*-isoindole-1,3(2*H*)-dione, 2-[[(1*R*,2*R*)-2-[[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]methyl]cyclohexyl]-methyl]hexahydro-, monohydrochloride (3a*R*,4*S*,7*R*,7a*S*)-; (2) (3a*R*,4*S*,7*R*,7*S*)-2-{(1*R*,2*R*)-2-[1,2-Benzisothiazol-3-yl)-piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione, hydrochloride. *CAS-367514-88-3; CAS-367514-87-2* [lurasidone]. *Treatment of schizophrenia* (*high-affinity agonist of serotonin 5-HT1A, 5-HT2, and 5-HT7 receptors as well as dopamine D2 receptors*). (Sumitomo) ✧*SM-13496*



Mitratapide [*2005*] (mit rat′ a pide). $C_{36}H_{41}ClN_8O_4S$. 717.30. (1) 3*H*-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[(2*S*,4*R*)-2-(4-chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-[(1*R*)-1-methylpropyl]-; (2) (–)-4-[4-[4-[4-[[(2*S*,4*R*)-2-(4-Chlorophenyl)-2-[[(4-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]methyl-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-(1*R*)-1-methylpropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one. *CAS-179602-65-4*. INN. *Management of obesity in dogs.* (Janssen) ✧*R103757*

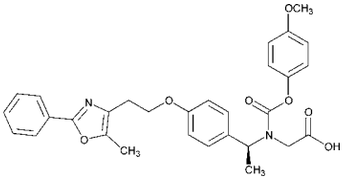


Netupitant [*2005*] (net ue′ pi tant). $C_{30}H_{32}F_6N_4O$. 478.61. (1) Benzeneacetamide, *N*,α,α-trimethyl-*N*-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-; (2) 2-[3,5-Bis(trifluoromethyl)phenyl]-*N*,2-dimethyl-*N*-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)-pyridin-3-yl]propanamide.*CAS-290297-26-6*. INN. *Antiemetic.* (Hoffmann-LaRoche) ✧*Ro 67-3189/000*

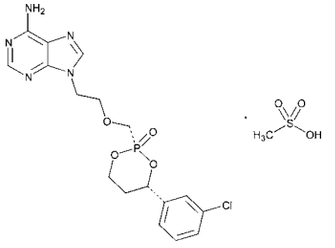


Ocrelizumab [*2005*] (oh kre liz oo mab). $C_{6494}H_{9978}N_{1718}O_{2014}S_{46}$. 148,000 daltons. Immunoglobulin G1, anti-(human CD20 (antigen)) (human-mouse monoclonal 2H7 γ1-chain), disulfide with human-mouse monoclonal 2H7 κ-chain, dimer. *CAS-637334-45-3*. *Treatment of rheumatoid arthritis.* (Genentech) ✧*PR070769*

Peliglitazar [*2005*] (pel ee gli′ ta zar). $C_{30}H_{30}N_2O_7$. 530.60. (1) Glycine,*N*-[(4-methoxyphenoxy)carbonyl]-*N*-[(1*S*)-1-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]ethyl]-; (2) [[(4-Methoxyphenoxy)carbonyl][(1*S*)-1-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]ethyl]amino]acetic acid. *CAS-331744-64-0*. INN. *Treatment of Type II diabetes mellitus, mixed dyslipidemia, atherosclerosis, and metabolic syndrome.* (Bristol-Myers Squibb) ✧*BMS-426707-1*

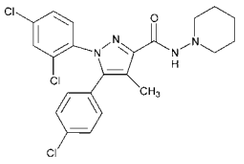


Pradefovir Mesylate [*2005*] (prad e foe′ veer). $C_{17}H_{19}ClN_5O_4P.CH_4O_3S$. 519.90. (1) 9*H*-Purin-6-amine, 9-[2-[[(2*R*,4*S*)-4-(3-chlorophenyl)-2-oxido-1,3,2-dioxaphosphorinan-2-yl]-methoxy]ethyl]-, monomethanesulfonate; (2) (2*R*,4*S*)-2-[[2-(6-Amino-9*H*-purin-9-yl)ethoxy]methyl]-4-(3-chlorophenyl)-1,3,2λ^5-dioxaphosphinan-2-one monomethanesulfonate. *CAS-625095-61-6*. *Antiviral.* (Valeant)

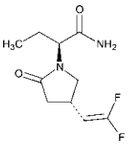


Prussian Blue Insoluble [*2005*] (prush′ un). $C_{18}Fe_7N_{18}$. 859.30. (1) Ferrate(4-), hexakis(cyano-κC)-, iron(3+) (3:4) (OC-6-11)-; (2) Ferric hexacyanoferrate (II). *CAS-14038-43-8*. *Antidote indicated in the treatment of patients with known or suspected internal contamination with radioactive cesium and/or nonradioactive thallium to increase their rates of elimination.* Antidotum-Thallii-Heyl (Heyl, Germany); Radiogardase-Cs (Fabrik GmbH & Co. KG, Germany)

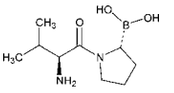
Rimonabant [*2005*] (rim′′ oh nab′ ant). $C_{22}H_{21}Cl_3N_4O$. 463.79. (1) 5-(*p*-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide; (2) 1*H*-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinyl. *CAS-168273-06-1*. INN. *Smoking cessation; treatment of obesity.* Acomplia (Sanofi-Synthelabo) ✧*SR141716*



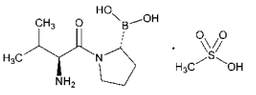
Seletracetam [*2005*] (sel′′ e tra′ se tam). $C_{10}H_{14}F_2N_2O_2$. 232.20. (1) 1-Pyrrolidineacetamide, 4-(2,2-difluoroethenyl)-α-ethyl-2-oxo-, (α*S*,4*S*)-; (2) (2*S*)-2-[(4*S*)-4-(2,2-Difluoroethenyl)-2-oxopyrrolidin-1-yl]butanamide.*CAS-357336-74-4*. *Treatment of epilepsy, hyperkinetic movement disorders.* (UCB Pharma, SA) ✧*ucb 44212*



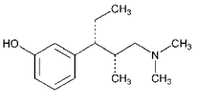
Talabostat [*2005*] (tal ab′ oh stat). $C_9H_{19}BN_2O_3$. 214.20. (1) Boronic acid, [(2*R*)-1-[(2*S*)-2-amino-3-methyl-1-oxobutyl]-2-pyrrolidinyl]-; (2) [(2*R*)-1-[(2*S*)-2-Amino-3-methylbutanoyl]pyrrolidin-2-yl]boronic acid. *CAS-149682-77-9*. INN. *Treatment of cancer; hematopoietic stimulant.* (Point Therapeutics) ✧*PT-100*



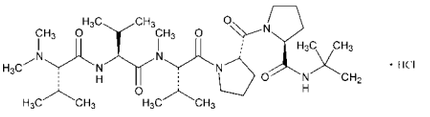
Talabostat Mesylate [*2005*] (tal ab′ oh stat). $C_9H_{19}BN_2O_3.CH_4O_3S$. 310.20. (1) Boronic acid, [(2*R*)-1-[(2*S*)-2-amino-3-methyl-1-oxobutyl]-2-pyrrolidinyl]-monomethanesulfonate; (2) [(2*R*)-1-[(2*S*)-2-Amino-3-methylbutanoyl]pyrrolidin-2-yl]boronic acid methanesulfonate. *CAS-150080-09-4*. *Treatment of cancer; hematopoetic stimulant.* (Point Therapeutics) ✧*PT-100*



Tapentadol [*2005*] (ta pen′ ta dol). $C_{14}H_{23}NO$. 221.34. (1) Phenol, 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]-; (2) 3-[(1*R*,2*R*)-3-(Dimethylamino)-1-ethyl-2-methylpropyl]phenol. *CAS-175591-23-8*. INN. *Analgesic* (μ-*agonist*). (Grünenthal GmbH, Germany) ✧*CG5503* (*base*); *BN 200* (*base*)



Tasidotin Hydrochloride [*2005*] (ta′′ si doe′ tim). $C_{32}H_{58}N_6O_5.HCl$. 643.30. (1) L-Prolinamide, *N*,*N*-dimethyl-L-valyl-L-valyl-*N*-methyl-L-valyl-L-prolyl-*N*-(1,1-dimethylethyl)-, monohydrochloride; (2) *N*,*N*-Dimethyl-L-valyl-L-valyl-*N*-methyl-L-valyl-L-prolyl-*N*-(1,1-dimethylethyl)-L-prolinamide monohydrochloride. *CAS-623174-20-9*. *Treatment of patients with advanced, refractory neoplasms* (*microtubule stabilizing agent*). (Ilex) ✧*ILX651*



Zanolimumab [*2005*] (zan oh lim′ ue mab). Immunoglobulin, anti-(human CD4 antigen) (human monoclonal 6G5 heavy chain), disulfide with human monoclonal 6G5 light chain, dimer. Molecular weight is approximately 147,000 daltons. *CAS-652153-01-0*. INN. *Treatment of rheumatoid arthritis, psoriasis, cutaneous and peripheral T-cell lymphoma.* (DSM Biologics, Netherlands); (Statens Serum Institute, Denmark) ✧*MDX-016; HuMax-CD4*

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 68 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. 19, No. 1, 2005.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Abatacept	Exbivirumab	Maraviroc	Revaprazan
Acotiamide	Fampronil	Mecasermin Rinfabate	Rilpivirine
Alagebrium Chloride	Fidexaban	Milataxel	Ritobegron
Alglucosidase Alfa	Fingolimod	Mirococept	Robenacoxib
Armodafinil	Gadodenterate	Paclitaxel Ceribate	Rostafuroxin
Bamirastine	Gantacurium Chloride	Palosuran	Selodenoson
Befetupitant	Golimumab	Panitumumab	Taltobulin
Belotecan	Idronoxil	Pegamotecan	Tandutinib
Carmoterol	Imiglitazar	Pelitinib	Teglicar
Cetilistat	Indacaterol	Perflubutane	Telavancin
Dasantafil	Indibulin	Perzinfotel	Tifuvirtide
Delucemine	Ismomultin Alfa	Prasugrel	Tilarginine
Denufosol	Lanimostim	Radafaxine	Topilutamide
Depelestat	Lemuteporfin	Ranirestat	Torapsel
Dirlotapide	Lenalidomide	Regadenoson	Trodusquemine
Edaglitazone	Lestaurtinib	Reparixin	Vandetanib
Eslicarbazepine	Libivirumab	Retapamulin	Vestipitant

United States Adopted Names (USAN) Under Consideration

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, Associate Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Nomenclature

USAN Under Consideration	Category
Acaftadine Afavatadine Alacaftadine Avnactadine	*H1 receptor antagonist*
Adfilcon H Alifilcon H Paflufocon A-hem-iberfilcon A Paflufocon D-hem-iberfilcon A	*Rigid gas permeable contact lens material with a poly HEMA soft skirt (hybrid contact lens material)*
Aerofilcon Elvifilcon A Enifilcon A Hyperfilcon Miplofilcon A Oxsilfilcon Silfilcon Tepsifilcon A Tepsifilcon AA	*Hydrophilic contact lens material*
Alconazole Pirconazole Zoconazole	*Antifungal agent*
Aldismasem Imisopasem Modismasem Selanzymin Selezymin Selmimase Selmimetase Somimase Somimetase Sopasemim Manganese Sumimetase Suprozymin Zormimase	*Anti-inflammatory and antimicrobial; SOD mimetic*
Aliskiren Hemifumarate	*Essential hypertension*
Altamisate Altarmirsate Ambetisate Amyglybril Amytargam Betamilod Cosamisate Prevamilod Preveglybril Prevetargam Talamibril Disodium Tramiprosate Zeprotargam Zontargam	*Treatment of mild-to-moderate Alzheimer's disease, treatment of cerebral amyloid angiopathy (antiamyloidotic)*

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

USAN Under Consideration	Category
Aminakant	*Treatment of patients with atrial fibrillation and atrial flutter*
Cardoxinyl Hydrochloride	
Difenakant	
Hexodinyl Hydrochloride	
Mefenexane Hydrochloride	
Nefenakant	
Nexonokoc	
Vernakant	
Amyglybril	*Treatment of Secondary (AA) Amyloidosis*
Amytargam	
Eprodisate Disodium	
Fibramilod	
Fibritargam	
Prevamibril Disodium	
Prodisate Disodium	
Prosdisate Disodium	
Prevamilod	
Preveglybril	
Zontargam	
Aposepotide	*Treatment of metastatic hormone refractory prostate cancer (HRPC)*
Astematide	
Astepotide	
Meraposetide	
Metapotide	
Metavitide	
Araserton	*Treatment of obesity*
Atabiceron	
Loranseton	
Lubiceron	
Sabiceron	
Axomadol	*Treatment of pain*
Azoramib	*Treatment of keratinization disorders, acne, and psoriasis*
Zolramib	
Zoramib	
Becafilcon A	*Hydrophilic contact lens material*
Betafilcon A	
Omegafilcon A	
Zetafilcon A	
Bedoradrine Sulfate	*Treatment of preterm labor; acute management of imminent preterm birth*
Cinovadrine	
Deleradrine Sulfate	
Mednovadrine	
Netaladrine Sulfate	
Befetupiant	*Treatment of depression*
Befetupitant	
Benatadine Dihydrochloride	*Treatment of atopic dermatitis*
Piratadine Dihydrochloride	
Zoltadine Dihydrochloride	
Zoratadine Dihydrochloride	
Brilapladib	*Treatment of atherosclerosis*
Darlipladib	
Brilipladib	*Treatment of atherosclerosis*
Corbilipladib	
Goxalapladib	
Orbilipladib	

USAN Under Consideration	Category
Canampanel	*Treatment of migraines and neuropathic pain*
Gisampanel	
Iquinglurant	
Tetrazoglurant	
Tezampanel	
Casipitant Mesylate	*Treatment of depression, anxiety, sleep disorders, nausea and vomiting, functional dyspepsia, Irritable Bowel Syndrome, gastroesophageal reflux disease, and overactive bladder disease*
Clasipitant Mesylate	
Cerlabulin Hydrochloride	*Antitumor; treatment of solid tumors*
Daibulin	
Davabulin Hydrochloride	
Novabulin	
Sovebulin Hydrochloride	
Corisbamate	*Treatment of epilepsy*
Coristamate	
Gorisbamate	
Goristamate	
Cribavirin	*Antiviral; prodrug of ribavirin*
Locarabine	
Paribavirin	
Patarabine	
Pribavirin	
Tepribavirin	
Vabavirin	
Viramidine	
Custaursapib	*Treatment of Parkinson's disease*
Custaurtinib	
Kaystaursapib	
Nurastarsapib	
Nurastaurtinib	
Nurstaursapin	
Staursapib	
Darlapladib	*Treatment of atherosclerosis*
Goxalipladib	
Oxalipladib	
Voxalipladib	
Denogliptin Tosylate	*Treatment of type 2 diabetes*
Dexamfetamine Lysine Dimesylate	*Treatment of ADHD (central nervous system stimulant)*
Dextroamphetamine Lysine Dimesylate	
Lidamfetamine Dimesylate	
Lidamphetamine Dimesylate	
Lidetamine Dimesylate	
Lidexamfetamine Dimesylate	
Lidextroamphetamine Dimesylate	
Lifentamine Dimesylate	
Lisamfetamine Dimesylate	
Dimethyl Fumarate	*Immunomodulator*
Necapimod	
Tenifimod	
Edaglitazone	*Treatment of type 2 diabetes*

USAN Under Consideration	Category
Elzivadose Hydrochloride Elzydavose Hydrochloride Fabenimose Hydrochloride	*Treatment of Fabry disease*
Emevatide Omatide Omevatide Vamevatide	*Melanoma peptide vaccine*
Fosaprepitant Dimeglumine	*Antiemetic; substance P antagonist (neurokinin NK1 antagonist)*
Ibuprofen Lysine	*Anti-inflammatory*
Larideprant Larideprast Larindeprant Larodeprant Larodeprast	*Treatment of prostaglandin mediated diseases*
Motovizumab Nolovizumab Numavizumab Ralivizumab Reslivizumab Resyvizumab Umavizumab	*Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk*
Ologlifozin Ologlisec Olonaglitib Sergliflozin Serglisec Sernaglitib Tranoglisec	*Treatment of type 2 diabetes mellitus as monotherapy and in combination with other glucose lowering agents*
Onsifocon B	*Hydrophobic contact lens*

USAN Under Consideration	Category
Oraptoclax Mesylate Raptobeclib Mesylate	*Antitumor*
Papahisperin Papifutespen Verpasep Caltespen	*Treatment of diseases caused by human papilloma virus (antiviral)*
Prexanavir	*Treatment of HIV infection*
Primilast Promilast Rimilast Zomilast	*Treatment of atopic dermatitis*
Robiceron Hydrochloride Robicotan Hydrochloride Vabiceron Hydrochloride Vabicotan	*Treatment of schizophrenia*
Rotiregap	*Treatment of ventricular tachycardia*
Sentricalamik Sentrigardib Sentrigardoc	*Gardos channel inhibitor*
Sevelamer Carbonate	*Treatment of renal failure*
Talabostat Mesylate	*Antineoplastic; hemotopoetic stimulant*
Valpreotide Acetate	*Treatment of acute variceal bleeding related to portal hypertension*
Vatuxumab Vicatuximab Voratuximab	*Anticancer*

International Nonproprietary Names (INN) Under Consideration

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 ensures 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.

(INN) Under Consideration	Category
Acaftadine	*H1 receptor antagonist*
Adatrioxolane Bispiroxolane Synperoxolane	*Antimalaria*
Adsoferan Curbosfal Spherical Adsorptive Carbon	*Adsorption of uremic toxins in the treatment of patients with chronic renal failure*
Akunatrib Atulinotrib Poladritrib	*Inhibition of PARP for the treatment of cancer*
Albagovomab	*Ovarian tumors*
Altabegron Amibegron Tanabegron Valabegron Zalibegron	*Antidepressant*
Altricinod Endakucinod Pranacinod	*Treatment of osteoarthritis*
Aposartan Famasartan Suprosartan	*Antihypertensive effect by blockade of the Angiotensin AT1 receptor*
Aptacept Aptranacept Trancacept	*Treatment of systemic lupus*
Arpadeporfin Azopadporfin Padeliporfin Stapadeporfin Zepadporfin	*Ophthalmology*
Avasizotine Mesylate	*Antidepressant*
Axitinib	*Antineoplastic-inhibitor of VEGF/PDGF receptor tyrosine kinases*
Bicamilast Sodium Glemilast Sodium Indomilast Sodium	*Treatment of inflammatory diseases*
Bosatinib	*Treatment of cancer*
Brilapladib	*Treatment of atherosclerosis*
Casarabine Cyclarabine Saparabine	*Treatment of cancer*
Casipitant Mesylate	*Treatment of depression, anxiety, sleep disorders, nausea and vomiting, functional dyspepsia, Irritable Bowel Syndrome, gastro-esophageal reflux disease, and overactive bladder disease*
Citilimumab	*Treatment of cancer*
Collacatib Duracatib Selcatib	*Antibone resorption agent*
Corglitazar Evoglitazar Vedaglitazar	*Dyslipidemic, antidiabetic, and anti-obesity*
Darlapladib	*Treatment of atherosclerosis*
Dasatinib	*Treatment of cancer*
Denogliptin Tosylate	*Treatment of type 2 diabetes*
Dimethyl Fumarate	*Immunomodulator*
Disomevatide	*Melanoma peptide vaccine*
Elzivadose Hydrochloride	*Treatment of Fabry disease*
Flipovudine Livudine Thymivudine	*Treatment of HIV*

(INN) Under Consideration	Category
Flocaltrol Secorol Urocaltrol	*Treatment of BPH*
Fosaprepitant Dimeglumine	*Antiemetic; substance P antagonist (neurokinin NK1 antagonist)*
Fospropofol Disodium	*Sedative-hypnotic*
Fungictumab Hesptumab Myctumab	*Treatment of Disseminated Candidal Infection*
Goxalapladib	*Treatment of atherosclerosis*
Incyplemib	*Treatment of rosacea and acute respiratory stress*
Isovaleramide	*Anxiolytic, anticonvulsant, antispastic, antimigraine, mood stabilizer, analgesic*
Larataxel Motitaxel Potetaxel	*Antineoplastic agent*
Lidetamine Dimesylate	*Treatment of ADHD*
Lifafil Lifanafil Lifanfil	*Erectile dysfunction*
Lifindol	*Inhibitor of platelet adhesion to collagen/antithrombotic*
Masutilukast Moderlukast Simalukast	*Treatment of asthma*
Mavacoxib	*Treatment of pain, inflammation, and fever*
Misotaxel	*Treatment of breast cancer*
Motovizumab	*Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk*
Nifiprevir Taliprevir Traliprevir	*Treatment of hepatitis C*
Noxad Noxal Xadiz	*Treatment of Alzheimer's disease*
Omevatide	*Melanoma peptide vaccine*
Oraptoclax Mesylate	*Antitumor*
Orvepitant Hydrochloride	*Treatment of depression, anxiety, and insomnia disorders*
Paladenoson	*Adjunct to nuclear myocardial perfusion imaging in patients unable to exercise adequately*
Pazopanib Hydrochloride	*Antineoplastic agent*
Pelaviroc Hydrochloride	*Treatment of HIV infection*
Prexanavir	*Treatment of HIV infection*
Prorelix Acetate	*Prostatic carcinoma, mammary carcinoma, uterine fibroids, endometriosis, benign prostate hyperplasia; GnRH antagonist*
Relamostat	*Treatment of osteoporosis*
Rotiregap	*Treatment of ventricular tachycardia*
Sitagliptin	*Treatment of type 2 diabetes mellitus and related disorders*
Sotirimod	*Treatment of dermatologic diseases, including actinic keratosis, infections, cancer*
Stamulumab	*Treatment of muscular dystrophy and age-related sarcopenia or frailty*
Tiratumumab	*Treatment of relapsed or refractory CD30 positive lymphoma*
Velafermin	*Treatment and/or prevention of mucositis*
Zendifentan Zibotentan Zifobentan	*Prostate cancer*

Nomenclature

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 31(1).

[*Note—This index covers Vol. 31 No. 1, pp. 1–288, Vol. 31, No. 2, pp. 289–669, Vol. 31, No. 3, pp. 671–980, Vol. 31, No. 4, pp. 981–1287*]

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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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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:

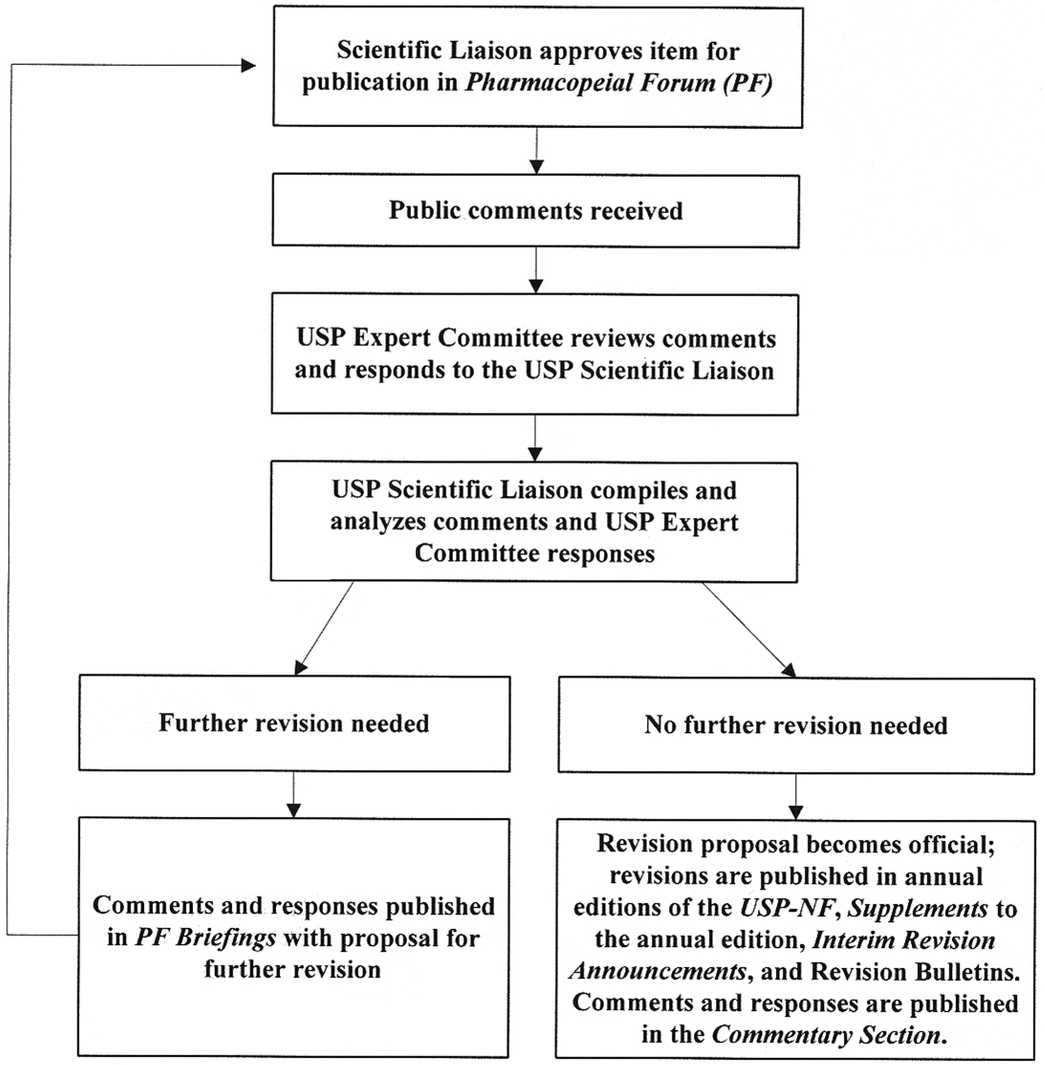
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official 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 *USP-NF* Standards Development



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@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 content of the different sections of *PF* are briefly described below. 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 in the *Guideline for Submitting Requests for Revision to the USP-NF* on the USP website (http://www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP-NF*

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 working 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.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

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
- Where to find 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* 31(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:

2000—2005

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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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 7a—Antibiotics; 7b—Antimicrobials and Antivirals
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

2005—2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell and Gene Therapy
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding

2005—2010 *(continued)*

RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005-2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Ph.D., Scientist	cma@usp.org	(301) 816-8139	Monograph Development—Cough, Cold and Analgesics (MD-CCA); Ophthalmology, Oncology, and Dermatology (MD-OOD)
Shawn C. Becker, BSN., Director, Patient Safety	scb@usp.org	(301) 816-8216	Safe Medication Use
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Evelyn Bryant, Manager, Editorial Services	eb@usp.org	(301) 816-8302	
Damian A. Cairatti, Senior Scientific Associate	dac@usp.org	(301) 816-8703	USP Spanish Edition; Dietary Supplements—Bioavailability (DS-BA); Dietary Supplements—General Chapters (DS-GC)
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Todd L. Cecil, Ph.D., Vice President, Standards Development	tlc@usp.org	(301) 816-8234	
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Behnam Davani, Ph.D., Senior Scientist	bd@usp.org	(301) 816-8394	Monograph Development—Antivirals and Antimicrobials (MD-AA)
Ian F. DeVeau, Ph.D., Acting Director, Complex Actives	ifd@usp.org	(301) 816-8178	Veterinary Drugs (VET); Veterinary Medicine Information (VMI)
Lawrence Evans, Ph.D., Scientist	le@usp.org	(301) 816-8389	Dietary Supplements—General Chapters (DS-GC); Dietary Supplements—Non-Botanicals (DSN)
L. Valentin Feyns, Ph.D., Scientific Fellow	lvf@usp.org	(301) 816-8121	Reference Standards (RS)

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Brian D. Gilbert, Ph.D., Scientist	bg@usp.org	(301) 816-8223	Monograph Development—Antibiotics (MD-ANT)
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Desmond G. Hunt, Ph.D., Senior Scientific Associate	dgh@usp.org	(301) 816-8341	Packaging and Storage (P&S)
James W. Kelly, Ph.D., Scientist	jwk@usp.org	(301) 816-8167	Parenteral Products—Industrial (PPI)
Christina H. Lee, Ph.D., Senior Scientific Associate	chl@usp.org	(301) 816-8335	Compounding Pharmacy (CRX); Sterile Compounding (SCC)
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Claudia C. Okeke, Ph.D., Associate Director, General Policies and Requirements Division	cco@usp.org	(301) 816-8243	Compounding Pharmacy (CRX); Parenteral Products—Compounding and Preparation (PPC); Sterile Compounding (SCC)
Horacio Pappa, Ph.D., Scientist and Latin American Liaison	hp@usp.org	(301) 816-8319	General Chapters (GC); Statistics (STAT)
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David A. Porter, Ph.D., Director,General Policies and Requirements	dap@usp.org	(301) 816-8225	

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Andrzej Wilk, Ph.D., Scientist	aw@usp.org	(301) 816-8305	Radiopharmaceuticals and Medical Imaging Agents (RMI); Radiopharmaceutical Information (RI)
Kahkashan Zaidi, Ph.D., Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER) General Chapters (GC)

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.

***PHARMACOPEIAL FORUM* COMMENT PERIOD EXTENDED.** USP is pleased to announce that the comment periods for *PF* proposals targeted for the *USP–NF* and its *Supplements* have been extended. The change in comment period timing is in response to stakeholder requests (see the *PF* 31(2) *Stimuli* article, *"The USP Revision Process: Recommendations for Enhancements"*). As a result of this change, industry now will have at least 90 days to comment on PF proposals, as opposed to the 60 day period previously provided.

Please note, however, that as a result of this transition, there will be a change to the comment deadline for *First Supplement* to *USP 29–NF 24,* which is being moved from October 15, 2005 to **August 15, 2005.** The original deadline of October 15, 2005 was based on the fact that both *PF* 31(3) and *PF* 31(4) would be included in the *First Supplement,* and the need to provide a sufficient comment period for the monographs contained in *PF* 31(4). With the transition to the 90-day review period, *PF* 31(4) is now being moved to the *Second Supplement* (with a comment deadline of December 16, 2005), and only *PF* 31(3) will be included in the *First Supplement.* Changing the deadline for the *First Supplement* to August 15, 2005 will still allow for a 90-day comment period for the monographs in *PF* 31(3), yet also will ensure that USP has enough time internally to fully review and consider all comments we receive and conduct the appropriate balloting process with USP's Expert Committees.

The complete revised Publication and Comment Schedule for *USP 29–NF 24* is outlined below, and includes the PFs, their corresponding targeted official publication, and the comment deadline.

Pharmacopeial Forum	Targeted Official Publication	Comment Deadline
PF 31(3)	*First Supplement to USP 29–NF 24*	August 15, 2005
PF 31(4) and *PF* 31(5)	*Second Supplement to USP 29–NF 24*	December 16, 2005
PF 31(6) and *PF* 32(1)	*USP 30–NF 25*	To be announced
PF 32(2) and *PF* 32(3)	*First Supplement to USP 30–NF 25*	To be announced
PF 32(4) and *PF* 32(5)	*Second Supplement to USP 30–NF 25*	To be announced
PF 32(6) and *PF* 33(1)	*USP 31–NF 26*	To be announced

If you have any difficulties in meeting the change in the deadline, please forward an "Intent to Comment" form (attached) to the USP Executive Secretariat or send an e-mail to the assigned Scientific Liaison.

Please direct any comments and questions on this topic to Todd L. Cecil, Ph.D., Vice President, Standards Development (301-816-8234 or tlc@usp.org) or Angela G. Long, Vice President, Volunteer and Organizational Affairs/Executive Secretariat (301-816-8382 or agl@usp.org).

USP TO DISCONTINUE POSTING LABELING CHANGES TO ⟨11⟩ *USP REFERENCE STANDARDS* IN *IRAS.* Beginning with this issue of *Pharmacopeial forum* [31(5)], USP will no longer print labeling changes to General Chapter ⟨11⟩ *USP Reference Standards* as an *Interim Revision Announcement*. The reason for the change is that, as stated in the General Chapter ⟨11⟩ *Reference Standards,* "Where, in an isolated instance, the specific label instruction differs from the text [presented in the chapter], the instructions on the label of the item from the current lot takes precedence. A situation may be infrequently encountered where it is necessary, on scientific grounds, to effect immediately a change in the instructions. This change can be made easily on the label of the Reference Standard, whereas the formal process for revising the compendial text requires more time." To summarize, the actual label text always takes precedence over General Chapter ⟨11⟩.

This change is a result of stakeholder comments that this USP practice causes confusion among *USP–NF* users. USP is exploring the potential of posting such information to the website on an information-only basis. USP welcomes user comments. Please submit them to the USP Executive Secretariat (execsec@usp.org).

USP REVISION CYCLE CHANGE. The 2005–2010 USP Revision Cycle has begun, and you will notice several changes in the *PF.* First of all, new Standards Expert Committees have been elected and are in the process of holding their first meetings. The list of chairs and members appears on USP's website at http://www.usp.org/aboutUSP/governance/expertList.html. Several Expert Committee names (and acronyms) have changed (see the list on page 1301). You also will note new Scientific Liaison assignments. This list appears on pages 1303–1305.

PQRI TO SURVEY CURRENT EXCIPIENT CONTROL PRACTICES. A working group of the Product Quality Research institute (PQRI), the joint government/industry/academia research consortium, plans to separately survey U.S. pharmaceutical manufacturers, excipient producers, and excipient distributors for information regarding companies' current excipient control practices to assure excipient safety, quality, and processability. Each survey will be confidential and respondents will not be asked to identify themselves, only their area of business, e.g., finished drug manufacturer, excipient manufacturer, or distributor. information received will be compiled by the PQRI Executive Secretariat and survey replies will not be reviewed by working group members, regardless of their affiliation.

It is hoped that information gathered will provide a more comprehensive view of the types of testing, compendial and noncompendial, which are currently in use throughout the different industry segments to control the chemical and physical properties of materials used in pharmaceutical manufacturing. It is anticipated that this information might be useful in connection with ongoing global harmonization efforts related to setting excipient specifications and determination of an excipient's processability. If so, all parties involved in PQRI activities will benefit, e.g., industry groups, the USP, and the FDA.

Subscribers to *Pharmacopeial Forum* and *USP–NF* are asked to watch for the forthcoming survey and to respond. As noted above, all responses will be blinded and confidential.

CORRECTION. *The Stimuli to the Revision Process* article (see page 2254 of *PF* 30(6) [Nov.–Dec. 2004]): *The FDA Process Analytical Technology (PAT) Initiative—An Alternative Pharmaceutical Manufacturing Practice (aPMP),* inadvertently included the acknowledgements section in the Author byline; the author byline and the acknowledgements sections should be: Authors: Walter Dziki and Gary E. Ritchie* Acknowledgements: USP Project Team 18—Process Analytical Technology (PAT)-Zhijun Jiang, David A. Radspinner, Michael Miller, Roger Deschenes, Paul Newby, Jeanne Moldenhauer, Claude Anger, Scott Sutton, Tony Cundell, Patrick McCarthy, Amy McDaniel, Stacy Montgomery, Claudio Denoya, Emil W. Ciurczak.

CALL FOR HIGH PRIORITY MONOGRAPHS FOR DRUG SUBSTANCES AND PRODUCTS, AND EXCIPIENTS. USP is seeking monographs for the following drug substances and drug products that are or, soon will be, off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monograph sponsors should consult USP's *Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/standards/revisionguideline/index.html.

For further information, contact Karen Russo, Ph.D., kar@usp.org.

Noncomplex Actives (Drug Substances and Products)

Noncomplex Actives (Drug Substances)		
Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine	Anagrelide Hydrochloride ***(Received)***	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bicalutamide ***(Received)***	Bivalirudin
Budesonide ***(Received)***	Cabergoline	Calcipotriene
Calcium Trisodium Pentetate	Calfactant	Candesartan Cilexetil
Carmustine ***(Received)***	Carvedilol	Cefdinir
Cefditoren Pivoxil	Ceftibuten	Cetirizine Hydrochloride
Cetrorelix	Cevimeline	Chloroxine
Cilostazol ***(Received)***	Citalopram Hydrobromide ***(Received)***	Colfosceril
Cytarabine Liposome	Dalfopristin	Dantrolene Sodium ***(Received)***
Dapirazole Hydrochloride	Desirudin	Dexrazoxane
Didanosine ***(Received)***	Difloxacin Hydrochloride	Divalproex Sodium ***(Received)***
Docosanol	Entacapone	Epoprostenol
Erythromycin Phosphate	Erythromycin Thiocyanate	Esomeprazole Magnesium
Esmolol	Estazolam	Estramustine Phosphate Sodium
Estradiol Benzoate	Ethanolamine Oleate	Etomidate
Etoposide Phosphate	Exemestane	Felbamate

Noncomplex Actives (Drug Substances and Products) *(Continued)*		
Fentanyl ***(Received)***	Fluoromethane F 18	Foscarnet Sodium
Fosfomycin Tromethamine	Gadobenate Dimeglumine	Galantamine
Gadopentetic Acid	Gallium Nitrate	Ganirelix
Glyceryl Aminobenzoate	Granisetron	Halobetasol Propionate
Haloperidol Decanoate	Hydrocodone Polistirex	Hydrocortisone ***(Received)***
Ibandronate Sodium	Imipramine Pamoate	Imiquimod
Irinotecan	Isosulfan Blue	Itraconazole
Lamotrigine	Latanoprost	Lawsone
Levetriacepam	Levobetaxolol	Levocabastine Hydrochloride
Levofloxacin ***(Received)***	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Miglitol	Mifepristone	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide	Nedocromil
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium	Orbifloxacin
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pancuronium Bromide ***(Received)***
Pantoprazole Sodium	Pemoline	Pentamidine Isethionate
Piperonyl Butoxide	Pirbuterol Acetate	Poractant Alpha
Prednicarbate ***(Received)***	Proguanil	Quetiapine Fumarate
Risperidone ***(Received)***	Rose Bengal	Salmeterol Xinafoate
Simethicone ***(Received)***	Sodium Phenylbutyrate	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride	Terconazole	Tiludronate Disodium
Tiopronin	Tranexamic Acid	Trimipramine Maleate
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate
Noncomplex Actives (Drug Products)		
Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Amlodipine and Benazepril Hydrochloride Capsules	Aminopterin Sodium Tablets
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution
Bivalirudin Injection	Budesonide Metered-Dose Inhalation Aerosol	Budesonide Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochlorides Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules

Noncomplex Actives (Drug Substances and Products) *(Continued)*

Butalbital and Acetaminophen Tablets	Butorphanol Tartrate Nasal Solution ***(Received)***	Calcipotriene Topical Solution
Cabergoline Tablets	Calcipotriene Cream	Calcipotriene Ointment
Calcitriol Capsules	Calcitriol Oral Solution	Calcium Acetate Capsules
Calfactant Intratracheal Suspension	Calcium Trisodium Pentetate Injection	Carbidopa and Levodopa Extended-Release Tablets
Carbidopa and Levodopa Tablets for Oral Suspension	Carbidopa, Levidopa, and Entacapone Tablets	Carmustine Implant
Carmustine for Injection	Carvedilol Tablets	Cefditoren Pivoxil Tablets
Cefdinir Tablets	Ceftibuten Capsules	Ceftibuten for Oral Suspension
Cetirizine Hydrochloride Oral Solution	Ceftiofur Hydrochloride Oral Suspension	Cetrorelix Injection
Cetirizine Hydrochloride Tablets	Cevimeline Hydrochloride Capsules	Choline and Magnesium Salicylates Oral Solution
Chloroxine Cream	Chlorpromazine Hydrochloride Extended-Release Capsules	Ciclopirox Shampoo
Choline and Magnesium Salicylates Tablets	Choline Salicylate Oral Solution	Ciclopirox Topical Gel
Ciclopirox Topical Solution	Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Cilostazol Tablets
Cimetidine Oral Solution	Citalopram Hydrobromide Oral Solution	Citalopram Hydrobromide Tablets ***(Received)***
Ciprofloxacin Otic Solution	Cladribine Injection	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation
Clonazepam Orally-Disintegrating Tablets	Clemastine Fumarate Syrup	Clobetasol Propionate Gel
Clotrimazole and Betamethasone Dipropionate Lotion	Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets
Colfosceril and Tyloxapol Suspension	Colestipol Hydrochloride Tablets	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets
Compound Undecylenic Acid Cream	Compound Undecylenic Acid Topical Powder	Cyclosporine Modified Oral Solution
Cromolyn Sodium Metered-Dose Nasal Solution	Cyclosporine Modified Capsules	Cysteamine Bitartrate Capsules
Cyclosporine Ointment	Cyclosporine Topical Solution	Cytarabine Liposome Injection
Dantrolene Sodium Capsules ***(Received)***	Dalfopristin and Quinupristin Injection	Dapiprazole for Ophthalmic Solution
Dantrolene Sodium for Injection ***(Received)***	Dantrolene Sodium Oral Suspension	Desirudin for Injection
Desonide ***(Received)***	Desonide Cream	Dexrazoxane for Injection
Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable Emulsion
Diclofenac Sodium Ophthalmic Solution	Didanosine Chewable Tablets ***(Received)***	Didanosine for Oral Solution ***(Received)***
Diethylpropion Hydrochloride Extended-Release Tablets	Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets
Dihydroergotamine Mesylate Metered Spray	Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories
Diphenhydramine Hydrochloride and Acetaminophen Tablets	Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution
Dorzolamide Ophthalmic Solution	Doxacurium Chloride Injection	Doxepin Hydrochloride Cream
Doxycycline Oral Gel	Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection
Enalaprilat Injection	Enalapril Maleate and Diltiazem Maleate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Entacapone Tablets	Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection
Epoprostenol Injection	Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules
Estazolam Tablets	Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection

Noncomplex Actives (Drug Substances and Products) *(Continued)*

Etomidate Injection	Etidronate Disodium Injection Concentrate	Exemestane Tablets
Famotidine Injection	Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension
Felbamate Tablets	Fentanyl Lozenges	Fentanyl Transdermal System
Ferrous Fumarate and Docusate Sodium Extended-Release Capsules	Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets
Fluconazole Injection	Flunisolide Nasal Spray	Fluconazole Tablets
Flunisolide Inhalation Aerosol	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluticasone Propionate Inhalation Powder	Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets
Gadobenate Dimeglumine Injection	Gallium Nitrate Injection	Galantamine Hydrobromide Tablets
Ganirelix Acetate Injection	Ganciclovir Capsules	Gentamicin Sulfate Oral Solution
Gatifloxacin Injection	Gatifloxacin Tablets	Glipizide Extended-Release Tablets
Gentamicin Sulfate Soluble Powder	Glimepiride Tablets	Granisetron Tablets
Granisetron Injection	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution
Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Ointment
Halobetasol Propionate Cream	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution
Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrochlorothiazide Capsules
Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets	Hydrocortisone Butyrate Lotion
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	Hydrocortisone Acetate Rectal Foam Aerosol	Hydroquinone Lotion
Hydrocortisone Acetate Dental Paste	Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution
Ibuprofen Capsules	Ibandronate Sodium Tablets	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules
Ketoprofen Extended-Release Capsules	Ketotifen Fumarate	Ketotifen Fumarate Ophthalmic Solution
Ketoprofen Tablets	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Levetriacepam Tablets	Levobetaxolol Ophthalmic Suspension
Levocabastine Ophthalmic Suspension	Leucovorin Calcium for Injection	Levomethadyl Acetate Hydrochloride Oral Concentrate
Levofloxacin Solution	Lidocaine and Prilocaine Cream ***(Received)***	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder
Liothyronine Injection	Lisinopril and Hydrochlorothiazide Tablets	Lomustine Capsules
Lopinavir Capsule	Lopinavir Solution	Lopinavir and Ritonavir Solution
Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***	Loratadine Orally Disintegrating Tablets	Losartan Potassium Tablets
Mesalamine Suppositories	Methacholine Chloride for Inhalation Solution	Mesoridazine Besylate Concentrate
Mefloquine Hydrochloride Tablets	Methoxsalen Softgels	Methadone Hydrochloride Oral Concentrate
Melphalan for Injection	Metaraminol Bitartrate Injection	Methyclothiazide and Deserpidine Tablets
Methocarbamol and Aspirin Tablets	Metipranolol Ophthalmic Solution	Metronidazole Cream
Metronidazole Lotion	Metronidazole Extended-Release Tablets	Methylphenidate Hydochloride Chewable Tablets
Metronidazole Capsules	Midazolam Hydrochloride Injection	Metronidazole Hydrochloride for Injection

Noncomplex Actives (Drug Substances and Products) *(Continued)*

Miconazole Nitrate Topical Aerosol	Mifepristone Tablets	Miglitol Tablets
Milrinone Injection	Misoprostol Dispersion ***(Received)***	Misoprostol Tablets ***(Received)***
Mivacurium in Dextrose Injection	Mivacurium Injection	Moexipril Hydrochloride and Hydrochlorothiazide Tablets
Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution	Morphine Sulfate for Injection Concentrate
Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate	Morphine Sulfate Tablets
Mycophenolate Mofetil Tablets	Mycophenolate Mofetil Oral Solution	Mycophenolate Mofetil Capsules
Nalbuphine Hydrochloride Injection	Naproxen Extended-Release Tablets	Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution
Nalmefene Hydrochloride Injection	Nateglinide Tablets	Nedocromil Sodium Inhalation Aerosol
Neomycin Sulfate Oral Powder	Nevirapine Oral Suspension	Nicardipine Hydrochloride Capsules
Nilutamide Tablets	Nimodipine Capsules	Nisoldipine Extended-Release Tablets
Nitroglycerin Solution in Acrylic Adhesive	Nizatidine Tablets	Ofloxacin Injection
Ofloxacin in Dextrose Injection	Olopatadine Ophthalmic Solution	Olsalazine Sodium Capsules
Ondansetron Oral Solution	Ondansetron Tablets	Orbifloxacin Tablets
Orlistat Capsule ***(Received)***	Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Orphenadrine Citrate Extended-Release Tablets
Oxcarbazepine Suspension	Oxcarbazepine Tablets	Oxiconazole Cream
Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium Tablets	Pantoprazole Sodium for Injection
Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension	Pemirolast Potassium Ophthalmic Solution
Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution	Pentaerythritol Tetranitrate Extended-Release Capsules
Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation	Pentamidine Isethionate for Injection
Pentazocine Hydrochloride and Acetaminophen Tablets	Permethrin Cream	Phendimetrazine Tartrate Extended-Release Capsules
Phenobarbital Capsules	Phentermine Resin Complex	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules
Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Phentermine Resin Complex Capsules	Phosphate Oral Solution
Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment	Pilocarpine Hydrochloride Tablets
Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol	Povacrylate Solution
Poractant Alpha Supension	Porfimer Sodium for Injection	Povacrylate-Iodine Topical Solution
Povidone-Iodine Gauze	Povidone-Iodine Swabsticks	Povidone-Iodine Topical Aerosol Foam
Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets	Prazosin Hydrochloride and Polythiazide Capsules
Prednicarbate Cream	Prednicarbate Ointment ***(Received)***	Prednisolone Sodium Phosphate Oral Solution
Prochlorperazine Maleate Extended-Release Capsules	Progesterone Capsules	Promethazine Hydrochloride and Codeine
Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup
Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets
Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets
Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pyrilamine Maleate Injection
Quinidine Sulfate Injection	Ramipril Capsules	Ranitidine Capsules

Noncomplex Actives (Drug Substances and Products) *(Continued)*

Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets	Rimantadine Hydrochloride Oral Solution
Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets	Risperidone Tablets
Rivastigmine Tartrate Capsules	Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection
Ropinirole Hydrochloride Tablets	Rose Bengal Ophthalmic Solution	Rosiglitazone Maleate Tablets
Salicylic Acid and Sulfur Cleansing Lotion	Salicylic Acid and Sulfur Lotion	Salicylic Acid and Sulfur Shampoo
Salicylic Acid Cream	Salicylic Acid Ointment	Salmeterol Inhalation Aerosol
Salmeterol Xinafoate Inhalation Powder	Scopolamine Transdermal System	Selegiline Hydrochloride Capsules
Serpacwa Topical Cream	Sertraline Hydrochloride Oral Solution	Sibutramine Hydrochloride Capsules
Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Sodium Chlorophyllin Copper Complex Tablets
Sodium Iodide Injection	Sodium Phenylbutyrate Oral Powder	Sodium Phenylbutyrate Tablets
Sodium Phosphates for Oral Suspension	Sodium Phosphates Tablets	Sodium Salicylate and Sulfur Shampoo
Sterile Talc Aerosol	Streptozocin for Injection	Sucralfate Oral Suspension
Sulconazole Nitrate Cream	Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension
Sulfacytine Tablets	Sulfanilamide Vaginal Cream	Sulfasalazine Oral Suspension
Sumatriptan Tablets	Sulisobenzone Lotion	Sumatriptan Injection
Tacrolimus Capsules	Tacrolimus Ointment	Tacrolimus Injection
Tamsulosin Hydrochloride Capsules	Technetium Tc 99m Teboroxime Injection	Tenofovir Disoproxil Fumarate Tablets
Terbinafine Hydrochloride Cream	Terbinafine Tablets	Terbinafine Topical Solution
Terconazole Vaginal Cream	Terconazole Vaginal Suppositories	Testosterone Transdermal System
Tetracycline Hydrochloride Periodontal Fiber	Theophylline Extended-Release Tablets	Tioconazole Vaginal Ointment
Tiopronin Tablets	Tolnaftate Topical Aerosol Solution	Topiramate Capsules
Topiramate Tablets	Torsemide Injection	Torsemide Tablets
Trandolapril and Verapamil Hydrochloride Extended-Release Tablets	Trandolapril Tablets	Tranexamic Acid Injection
Tranylcypromine Sulfate	Tranylcypromine Sulfate Tablets	Tretinoin Capsules
Tretinoin Microsphere Gel	Triamcinolone Acetonide Metered-Dose Nasal Suspension	Trifluridine Ophthalmic Solution
Trimetrexate for Injection	Trimipramine Maleate Capsules	Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup
Trolamine Salicylate Cream	Trolamine Salicylate Gel	Trolamine Salicylate Topical Emulsion
Trovafloxacin Injection	Trovafloxacin Mesylate for Injection	Undecylenic Acid Topical Foam Aerosol
Unoprostone Isopropyl Ophthalmic Solution	Urea Cream	Valproic Acid Injection ***(Received)***
Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules	Venlafaxine Tablets
Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection
Voriconazole Oral Suspension	Voriconazole Tablets	Yttrium Y-90 Chloride Solution
Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection	Ziprasidone Hydrochloride Capsules
Zidovudine and Lamivudine Tablets	Zinc Acetate Capsules	Zoledronic Acid for Injection
Zinc Tridosium Pentetate Injection		

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	*N*-Acetyl Methionine
Aconitic Acid (Achilleic Acid)	Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal
Aliphatic Polyesters	Aluminum Ammonium Sulfate	Aluminum Hydroxide
Aluminum Lactate	Aluminum Oxide	Aluminum Ammonium Sulfate
Aluminum Potassium Sulfate	Aluminum Silicate	Aluminum Sodium Sulfate
Aluminum Stearate	Allantoin-Sodium Pyrrolidone Carboxylate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	Ascorbyl Stearate
Batylalcohol Monostearate	Benzododecinium Bromide	Benzyl Chloride
Benzyl Nicotinate	Brominated Vegetable Oil	Butadiene-Styrene Rubber
Beta Naphthol	Butylene Glycol	Butylphthalyl Butylglycolate
Butylated Hydromethylphenol	Calcium Alginate	Calcium Alginate and Ammonium Alginate
Calcium Acid Pyrophosphate	Calcium Chloride Solution	Calcium Glycerophosphate
Calcium Bromide	Calcium Phospahte Dibasic, Monohydrate	Calcium Phosphate Monobasic
Calcium Phosphate Dibasic, Anhydrous	Calcium Pyrophosphate	Calcium Sorbate
Calcium Propionate	Calcium Sulfate Dihydrate	Calcium Sulfate, Anhydrous
Calcium Stearoyl Lactylate	Calteridol Calcium	Canola Oil ***(Received)***
Caldiamide Sodium	Caprylic/Capric Diglyceril Succinate	Carbon
Capric Acid	Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium
Carboxymethyl Starch	Cetostearyl Isononanoate	Cholic Acid
Cinnamaldehyde	Chlorodifluoroethane	Cocamide Diethanolamine
Cocamide Oxide	Coconut Oil Hydrogenated	Cocoyl Caprylocaprate
Coconut Oil	Copper Sulfate	Crystal Gum
Cutina	Cystine	Cysteine Hydrochloride
Dammar Gum	Decanoic Acid	Decyl Oleate
Dehydroacetic Acid	Desoxycholic Acid	Dextrin Palmitate
Dextrins Modified	Diacetyl Tartaric Acid Esters of Mono- and Diglycerides	Dicetyl Phosphate
Dichlorofluoromethane	Diethylene Glycol Monopalmitostearate	Diethyl Sebacate
Difluoroethane	Diglycol Stearate	Diisopropanolamine ***(Received)***
Diisobutyl Adipate	Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide
Dilauryl Thiodipropionate	Dimethyl Dicarbonate	Dimyristoyl Lecithin
Dimyristoyl Phosphatidylglycerol	Dioctyl Sodium Sulfosuccinate	Dipropylene Glycol
Disodium Edisylate	Disodium Guanylate	Disodium Inosinate
Disodium Monooleamide Sulfasuccinate	Erythritol ***(Received)***	Erythorbic Acid
Erythrosine	Ethoxylated Mono- and Diglycerides	Ethoxyquin
Ethyl Hexanediol	Ethyl Linoleate	Ethyl Maltol
Ethylene Dichloride	Ethylene Glycol Monopalmitostearate	Ethylurea
Ferric Ammonium Citrate	Ferric Citrate	Ferric Oxide, Brown
Ferric Phosphate	Ferric Pyrophosphate	Ferrous Citrate
Ferrous Glycinate	Ferrous Lactate	Fluorochlorohydrocarbons
Formic Acid	Furcelleran	Gamma-Cyclodextrin
Gentistic Acid	Geraniol	Glutamic Acid
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydrogenated Starch Hydrolysate	Hydroxyethylmethylcellulose
Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin	Indigotine
Inositol	Iron Carbonyl	Iron Subcarbonate
Isobutylated-Isoprene Copolymer	Isooctylacrylate	Isopropyl Isostearate
Isopropyl Stearate	Isostearic Acid	Isostearyl Alcohol

Excipients *(Continued)*

Lactobionic Acid	Lactose Ferrin, Bovine	Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol
Lactylic Esters of Fatty Acids	Lanolin Anhydrous	Lanolin Alcohols, Acetylated
Lanolin (Wool Fat), Hydrogenated	Lanolin Hydrous	Lauramine Oxide
Lauric Acid	Lauric Diethanolamide	Lauric Myristic Diethanolamide
Lavender Oil	Lecithin, Hydroxylated	Leucine
Linoleic Acid	Macrogol Lauryl Ether	Macrogol Oleate
Macrogol Sorbitan Tristearate	Macrogol Stearyl Ether	Macrogolgrycerol Cocoates
Macrogolgrycerol Triisostearate	Magnesium Aluminum Silicate Hydrate	Magnesium Aspartate
Magnesium Aspartame Dihydrate	Magnesium Phosphate, Diabasic, Trihydrate	Magnesium Tartrate
Maltitol ***(Received)***	Maltitol Syrup	Maltol Isobutyrate
Malt Syrup	Manganese Chloride	Manganese Citrate
Manganese Glycerophosphate	Manganese Hypophosphite	Mannose
Medical Antifoam Emulsion C	Medronate Disodium	Medronic Acid
Methyl Chloride	Methylchloroisothiazolinone	Methyl Hydroxyethyl Cellulose
Methylisothiazolinone	*N*-Methylpyrrolidone ***(Received)***	Microcrystalline Cellulose, Silicified
Mineral Spirits	Monoisostearyl Glyceryl Ester	Monopotassium Glutamate Monohydrate
Monosodium Citrate	Mullein Leaf	Myristyl Gamma-Picolinium Chloride
Myristyl Lactate	*N*,*N*-Bis(2-Hydroxyethyl)Stearamide	Naphtha
Nonpareil Seeds	Nutmeg Oil	Octanoic Acid
Oleyl Oleate	Oxystearin	Palm Kernel Oil
Palm Oil	Pentasodium Triphosphate	Pentetate Calcium Trisodium
Pentetate Pentasodium	Phenprobamate	Phenylmercuric Borate
Pine Oil	Polacrilin	Polyacrylate Dispersion 30 Percent ***(Received)***
Polydextrose	Polydextrose Solution	Polyglycerol Esters of Fatty Acids
Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil—(USP has 35)	Polyoxyl Stearate -(USP has 40)
Polypropylene Oleate	Polyvinyl Acetate	Polyvinylacetal
Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone	Polypropylene Stearyl Ether
Polyvinylpyrrolidone Ethylcellulose	Polysorbate 65	Potassium Acid Tartrate
Potassium Alginate ***(Received)***	Potassium Bromate	Potassium Carbonate Solution
Potassium Dichloroisocyanurate	Potassium Gibberellate	Potassium Glycerophospate
Potasssium Iodate	Potassium Nitrite	Potassium Phosphate
Potassium Phosphate Tribasic	Potassium Polymetaphosphate	Potassium Pyrophosphate
Potassium Stearate	Potassium Sulfate	Potassium Sulfite
Potassium Tripolyphosphate	Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters
Propylene Glycol Monolaurate ***(Received)***	Propyl Propionate	Purified Polyoxyl 35 Castor Oil ***(Received)***
Rapeseed Oil, Hydrogenated	Rapeseed Oil, Superglycerinated	Rice Bran Wax
Rosin	Silicone	Sodium Acid Pyrophosphate
Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic	Sodium Aluminum Phosphate Basic
Sodium Aspartate	Sodium Bisulfate	Sodium Bisulfite
Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan	Sodium Caseinate
Sodium Chlorate	Sodium Citrate, Dibasic	Sodium Dehydroacetate
Sodium Diacetate	Sodium Erythorbate	Sodium Ferric Pyrophosphate
Sodium Ferrocianide	Sodium Ferrocyanide	Sodium Hypophosphite
Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate
Sodium Magnesium Silicate	Sodium Malate	Sodium Metaphosphate, Insoluble
Sodium Metasilicate	Sodium Methylate	Sodium Polyphosphates Glassy
Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate
Sodium Sesquicarbonate	Sodium Sesquinoleate	Sodium Stearoyl Lactylate
Sodium Thiomalate	Sodium Trimetaphosphate	Sodium Trioleate
Sodium Tripolyphosphate	Soy Polysaccharides	Stannous Chloride

Excipients *(Continued)*

Stannous Tartrate	Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca
Stearalkonium Chloride	Stearyl Citrate	Stearyl Monoglyceridyl Citrate
Succinylated Monoglycerides	Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters
Sucrose Stearate	Sucrose Syrup	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tall Oil	Tallow
Tallow Glycerides	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetereth-4 Phosphate
Trichloethylene	Trichloroethylene	Trimyristin
Trisidium Citrate	Trolamine Lauryl Sulfate	Vegetable Oil
Wheat Flour	Wheat Germ Oil	Wheat Gluten
Whey		

USP ANNUAL SCIENTIFIC MEETING, SEPTEMBER 27–30, 2005: IMPACT THE FUTURE OF PHARMACOPEIAL STANDARDS. The USP Annual Scientific Meeting will be held in the Hotel del Coronado, Coronado, California, September 27–30, 2005.

Spread the word. Tell your colleagues and register at: www.usp.org/conferences, 301-816-8134.

The USP 2005 Annual Scientific Meeting is your opportunity to directly contribute to USP's standards-setting processes. Through interaction with USP's scientific staff and Council of Experts, you will help establish standards-setting priorities for the organization and help shape the quality requirements that you must, by law, follow.

Meeting tracks include:

Analytical Validation and Verification of Compendial Methods

Learn about the new USP information in General Information Chapter ⟨1226⟩ *Verification of Compendial Procedures.* This track also includes presentations and workshops on the requirements for evolving analytical validation procedures, including spectroscopic and other physical test methods.

Biologics and Biotechnology Derived Therapies

Interactive discussion on cross-cutting, standards-setting activities currently being undertaken by USP, including validation of bioassays, development of standards for ancillary materials and international activities in biological standardization.

Dietary Supplements

Learn about the current and future impact of dietary supplement verification and new FDA regulatory initiatives on the marketplace; expansion of General Information Chapter ⟨2030⟩ *Supplemental Information for Botanicals;* technologies for botanical classification; and identification and analysis of new/emerging/potential dietary supplement ingredients.

Excipients

Interact with USP scientific experts, FDA, industry, and academic experts to discuss the science and related issues of excipients quality, including additives, excipient functionality and its impact on formulation, and multisource excipient equivalence, as well as recent advances in the development of novel excipients.

Making *USP–NF* Work for You

Be among the first to learn about future directions and updates based on resolutions adopted at the 2005 USP Convention and through other USP initiatives.

Annual Scientific Meeting 2005 Exhibit Program

Network with your colleagues as they showcase what's new and upcoming in the industry.

WHO SHOULD ATTEND:

- *USP–NF* and USP Reference Standards Users
- Scientists focusing on chemistry, biologics and biotechnology, analytical validation, excipients, and dietary supplements
- Government representatives
- Academia and association representatives
- Regulatory Affairs personnel
- R&D and QC personnel
- Lab supervisors/managers
- Compendial Affairs personnel
- Statisticians
- Technical consultants
- Healthcare practitioners

New and experienced bench chemists who want to better understand the USP process also may wish to attend the "Making *USP–NF* Work for You" track.

SCHEDULE:

Day 1—	September 27, 2005:	Registration
Day 2—	September 28, 2005:	The Annual Scientific Meeting starts with an opening session in the morning followed by Track Session I in the afternoon
Day 3—	September 29, 2005:	Track Session II (morning) and Track Session III (afternoon)
Day 4—	September 30, 2005:	Track Session IV in the morning followed by a "Town Hall" discussion. Meeting adjourns at 12:30 p.m.

Continuing Education

Extension Services in Pharmacy at the University of Wisconsin-Madison School of Pharmacy is accredited by the Accreditation Council on Pharmacy Education (ACPE, formerly the American Council on Pharmaceutical Education) as a provider of continuing pharmaceutical education. This program is approved for 14.5 hours or 1.45 continuing education units (CEUs).

In order to receive credit, pharmacists will be required to complete an Annual Scientific Meeting evaluation form. in addition, pharmacists must complete a statements of credit form for continuing pharmaceutical education participation which will be mailed (by USP) within one month after the meeting. ACPE numbers: 073-999-05-076-L04 through 073-999-05-081-L04.

ADVANCE NOTICE OF UPCOMING OFFICIAL REVISIONS TO THE *USP–NF*. In order to provide as much time as possible for industry to adopt revisions made to the compendia, upcoming official revisions to the *USP–NF* are now being announced on the USP website as soon as they are voted on to become official by the appropriate Expert Committees of the Council of Experts.

Readers are directed to the "Notices" section found in the top right corner of the USP homepage at www.usp.org. By clicking on "Upcoming official Revisions to the *USP–NF:* Reference Standards Required But Not Available," you are taken to a page where upcoming revisions to the compendia are listed. The information posted includes the title of the item being revised, the *PF* citation where the revision was proposed, and a description of the proposal. in addition, an e-mail link to the USP Scientific Liaison for each revision is listed in parentheses after the item. The actual content and official date of each revision will be published in either an annual edition, *Supplement,* or *Interim Revision Announcement* and the items are sorted according to the publication in which they are to appear.

In addition, readers will also find a list of new USP Reference Standards that correspond to new *USP–NF* monographs but unfortunately are not yet available. The official dates of any *USP–NF* Standards, tests, or assays that require the use of these Standards are postponed until further notice pending availability of the Standards.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE *USP–NF*. The *USP Guideline for Submitting Requests for Revision to the USP–NF* is available on USP's website at www.usp.org. 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 Noncomplex 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 on the USP website at www.usp.org/USPNF/submitmonograph/subGuide.html. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2005 are listed below. for more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

2005 Calendar of Pharmacopeial Education Courses

Date	Name of Course	Location
Sept 19	Effectively Using the USP–NF	Royal College of Surgeons of Ireland (RCSI), Dublin
Sept 20	Analytical Method Validation	RCSI, Dublin, Ireland
Sept 21	Fundamentals of Microbiology	RCSI, Dublin, Ireland
Sept 21–22	Fundamentals of Dissolution, Lecture	RCSI, Dublin, Ireland
Sept 28–29	Fundamentals of Dissolution	Mexico City, Mexico
October (date TBD)	Fundamentals of Microbiology	Chicago, IL
October 13–14	Effectively Using the USP–NF	Munich, Germany
October 18–19	Fundamentals of Dissolution (Italian)	Basel, Switzerland
October 19–20	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
October 20–21	Fundamentals of Dissolution (French)	Basel, Switzerland
November 2–3	Fundamentals of Dissolution	USP Headquarters
November 4	Fundamentals of Microbiology	Southern California (location TBD)
December 5–6	Effectively Using the USP-NF	Brussels, Belgium
December 7	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 8	Standards 101: Advanced Use of *USP–NF,* General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
December 8–9	Effectively Using the USP–NF	Basel, Switzerland

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 PRINT, ONLINE, AND CD.** *USP–NF,* the authoritative reference for official pharmaceutical standards is available in three convenient formats—print, online, and CD. One main edition and two *Supplements* are published each year. The current edition, *USP 28–NF 23*, is official through 2005. Starting with the *Second Supplement* to *USP 28–NF 23,* the *USP–NF* Online and CD versions feature several enhancements. The enhancements include ''My *USP–NF,*'' an exciting new option that lets subscribers customize their use of *USP–NF* by saving frequent searches, creating a unique table of contents, and using other personalization options. The *USP29–NF24* will be published on November 1, 2005. Orders will be accepted starting on September 1. To order *USP–NF,* go to www.usp.org or call 1-800-227-8772 or 301-881-0666.

CHROMATOGRAPHIC REAGENTS. Official and proposed chromatographic procedures in the *USP–NF* and *Pharmacopeial Forum (PF)* refer to column reagents only by 'L,' 'S,' or 'G' designations. The brand names of these reagents are listed in *Chromatographic Reagents.* This book also provides an index of column manufacturers and lists alternative columns that may be used to carry out official procedures. *Chromatographic Reagents* saves chemists and scientists valuable laboratory time spent searching for the right columns to use in testing. *Chromatographic Reagents* is available in print format. The online format of the *USP–NF* includes the latest *Chromatographic Reagents*. To order *Chromatographic Reagents,* go to www.usp.org or call 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 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. 2005	Apr. 1, 2005
PF 31(2) [Mar.–Apr. 2005]	Mar. 2005	Not Applicable
2nd IRA [published in *PF* 31(2)]	Mar. 2005	Apr. 1, 2005
PF 31(3) [May–June 2005]	May 2005	Not Applicable
3rd IRA [published in *PF* 31(3)]	May 2005	June 1, 2005
2nd Supplement	June 2005	Aug. 1, 2005
PF 31(4) [July–Aug. 2005]	July 2005	Not Applicable
4th IRA [published in *PF* 31(4)]	July 2005	Aug. 1, 2005
PF 31(5) [Sept.–Oct. 2005]	Sept. 2005	Not Applicable
5th IRA [published in *PF* 31(5)]	Sept. 2005	Oct. 1, 2005
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005*	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005*	Dec. 1, 2005*
PF 32(1) [Jan.–Feb. 2006]	Jan. 2006*	Not Applicable
1st IRA [published in *PF* 32(1)]	Jan. 2006*	Feb. 1, 2006*
1st Supplement	Feb. 2006*	Apr. 1, 2006*
PF 32(2) [Mar.–Apr. 2006]	Mar. 2006*	Not Applicable
2nd IRA [published in *PF* 32(2)]	Mar. 2006*	Apr. 1, 2006*
PF 32(3) [May–June 2006]	May 2006*	Not Applicable
3rd IRA [published in *PF* 32(3)]	May 2006*	June 1, 2006*
2nd Supplement	June 2006*	Aug. 1, 2006*
PF 32(4) [July–Aug. 2006]	July 2006*	Not Applicable
4th IRA [published in *PF* 32(4)]	July 2006*	Aug. 1, 2006*
PF 32(5) [Sept.–Oct. 2006]	Sept. 2006*	Not Applicable
5th IRA [published in *PF* 32(5)]	Sept. 2006*	Oct. 1, 2006*
PF 32(6) [Nov.–Dec. 2006]	Nov. 2006*	Not Applicable
6th IRA [published in *PF* 32(6)]	Nov. 2006*	Dec. 1, 2006*

*Tenative

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 (*USP27*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 27*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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 28* and to *NF 23*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Eric B. Sheinin, Ph.D., *Chief Science Officer*

Official October 1, 2005 **Released September 1, 2005**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of *USF–NF* users.

USP Ademetione Disulfate Tosylate RS (January 1, 2006)
USP Adipic Acid RS (September 1, 2005)
USP Agnuside RS (November 1, 2005)
USP Aluminum Sulfate (AS)
USP Ammonium Phosphate Dibasic (AS)
USP Ascorbyl Palmitate RS (September 1, 2005)
USP Asparagine Anhydrous RS (November 1, 2005)
USP Asparagine Monohydrate RS (November 1, 2005)
USP Bismuth Subcarbonate RS (September 1, 2005)
USP Bismuth Subgallate RS (September 1, 2005)
USP Bismuth Subnitrate RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound A RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound B RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound C RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound F RS (January 1, 2006)
USP Calcium Stearate (AS)
USP Carboxymethylcellulose Calcium (AS)
USP Carboxymethylcellulose Sodium RS (September 1, 2005)
USP Carprofen RS (September 1, 2005)
USP Casticin RS (November 1, 2005)
USP Microcrystalline Cellulose (AS)
USP Powdered Cellulose (AS)
USP Ciclopirox RS (January 1, 2006)
USP Ciclopirox Related Compound A RS (January 1, 2006)
USP Ciclopirox Related Compound B RS (January 1, 2006)
USP Clopidogrel Bisulfate RS
USP Clopidogrel Bisulfate Related Compound A RS
USP Clopidogrel Bisulfate Related Compound B RS
USP Clopidogrel Bisulfate Related Compound C RS
USP Cromolyn Sodium Related Compound A (AS)
USP 2-Deoxy-D-glucose RS (November 1, 2005)
USP Desoaminylazithromycin RS (January 1, 2006)
USP Dibutyl Sebacate (AS)
USP Dichlorvos (AS)
USP Diethanolamine RS (November 1, 2005)
USP Eleutheroside B RS (January 1, 2006)
USP Eleutheroside E RS (January 1, 2006)
USP Enrofloxacin RS (January 1, 2006)
USP Eugenol RS (November 1, 2005)
USP Fludeoxyglucose Related Compound A RS (September 1, 2005)
USP Fluvoxamine Maleate RS (November 1, 2005)
USP L-Fucose RS (November 1, 2005)
USP Galactitol RS (January 1, 2006)
USP Indapamide Related Compound A (AS)
USP Indinavir RS (September 1, 2005)
USP Indinavir System Suitability RS (September 1, 2005)
USP Insulin Lispro RS
USP Isopropyl Alcohol RS (September 1, 2005)
USP Lactic Acid (AS)
USP Lauroyl Polyoxylglycerides (AS)
USP Lutein RS (September 1, 2005)
USP Magnesium Carbonate (AS)
USP Magnesium Stearate (AS)
USP Maltose Monohydrate RS (January 1, 2006)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Meglumine RS (September 1, 2005)
USP Melengestrol Acetate RS (September 1, 2005)
USP Melengestrol Acetate Related Compound A RS (September 1, 2005)
USP Melengestrol Acetate Related Compound B RS (September 1, 2005)
USP Metacholine Chloride (AS)
USP Methyl Salicylate RS (September 1, 2005)
USP Monobasic Potassium Phosphate (AS)
USP Monoethanolamine RS (November 1, 2005)
USP Monosodium Glutamate RS (September 1, 2005)
USP Morantel Tartrate RS (September 1, 2005)
USP Oleic Acid RS (November 1, 2005)
USP Olive Oil (AS)
USP Omeprazole Related Compound A RS (September 1, 2005)
USP Pancuronium Bromide RS (September 1, 2005)
USP Peanut Oil (AS)
USP Phenylethyl Alcohol RS (November 1, 2005)
USP Phosphoric Acid (AS)
USP Polyoxyl 20 Cetostearyl Ether RS
USP Polyoxyl 20 Stearyl Ether RS
USP Potassium Acetate (AS)
USP Potassium Bitartrate (AS)
USP Potassium Citrate RS (September 1, 2005)
USP Potassium Nitrate (AS)
USP Dibasic Potassium Phosphate (AS)
USP Potassium Sodium Tartrate RS (September 1, 2005)
USP Potassium Sorbate (AS)
USP Prilocaine RS (January 1, 2006)
USP Prilocaine Related Compound A RS (January 1, 2006)
USP Propofol RS (January 1, 2006)
USP Propofol Related Compound A RS (January 1, 2006)
USP Propofol Related Compound B RS (January 1, 2006)
USP Propofol Related Compound C RS (January 1, 2006)
USP Propofol Resolution Mixture C RS (January 1, 2006)
USP Ramipril Related Compound D RS (November 1, 2005)
USP Residual Solvent Class 2—Hexane RS (November 1, 2005)
USP Residual Solvents Class 2—Mixture B RS (January 1, 2006)
USP β-Sitosterol RS (September 1, 2005)
USP Sodium Bicarbonate (AS)
USP Sodium Benzoate RS (January 1, 2006)
USP Sodium Chloride (AS)
USP Sorbic Acid (AS)
USP Stavudine RS (January 1, 2006)
USP Stavudine System Suitability Mixture RS (January 1, 2006)
USP Sulfaquinoxaline Related Compound A RS (January 1, 2006)
USP Sumatriptan Succinate Related Impurities RS (November 1, 2005)
USP Tagatose RS (January 1, 2006)
USP Tannic Acid RS (September 1, 2005)
USP Tartaric Acid RS (September 1, 2005)
USP Terbutaline Related Compound A RS (September 1, 2005)
USP Thymol RS (November 1, 2005)
USP Tilmicosin RS (November 1, 2005)
USP Tolcapone Related Compound B RS (September 1, 2005)
USP Trenbolone CIII RS (November 1, 2005)
USP Trenbolone Acetate CIII RS (November 1, 2005)
USP Tribasic Calcium Phosphate (AS)
USP Trolamine RS (November 1, 2005)
USP Tylosin Tartrate RS (September 1, 2005)
USP Urea RS (September 1, 2005)

Unavailable First-Time Official Reference Standards

The official dates of any *USP 28* or *NF 23* 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 Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Berberine Chloride RS
USP Budesonide RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Cetrimonium Bromide RS
USP Copolymer Polypropylene RS
USP Cytosine RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluticasone Propionate Resolution Mixture RS
USP Fluticasone Propionate System Suitability Mixture RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Hydrastine Hydrochloride RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Mecamylamine Related Compound A RS
USP Mefloquine Hydrochloride RS
USP Mefloquine Related Compound A RS
USP Menotropins RS
USP Methyldopa-glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Related Compound A RS
USP Naratriptan Related Compound B RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Norphenylephrine Hydrochloride RS
USP Ondansetron RS
USP Paricalcitol Solution RS
USP Maritime Pine Extract RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Posterior Pituitary RS
USP Potassium Perchlorate RS
USP Proinsulin (Beef) RS
USP Proinsulin (Pork) RS
USP Propofol for System Suitability RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Ropivacaine Hydrochloride RS
USP Ropivacaine Related Compound A RS
USP Ropivacaine Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tiagabine Related Compound A RS
USP Racemic Tiagabine Hydrochloride Mixture RS
USP Tiagabine Hydrochloride RS
USP Tinidazole Related Compound B RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS

NOTICE OF POSTPONEMENT

Assay under *Vinorelbine Injection (First Supplement* to *USP 28–NF 23,* page 3281), pending development of a Vinorelbine Tartrate Reference Standard (RS) lot suitable for all official USP compendial applications

USP has **postponed indefinitely** the official date of the *Assay* under the *Vinorelbine Injection* monograph, which was published on page 3281 of the *First Supplement to USP 28–NF 23*. This postponement applies retroactively to the monograph's official date, April 1, 2005. All other portions of the monograph remain official.

This postponement allows USP to develop a lot of USP Vinorelbine Tartrate Reference Standard (RS) that is suitable for all official USP compendial applications. The current lot of USP Vinorelbine Tartrate RS (Lot F0C243) is suitable for qualitative testing purposes (including the qualitative testing required by the *Vinorelbine Tartrate* monograph) but is known to be unsuitable as currently labeled for the quantitative testing specified in the *Assay* under *Vinorelbine Injection.*

This postponement is consistent with the *General Notices* section of *USP 28–NF 23* relating to USP Reference Standards, which states the following:

> The requirements for any new *USP* or *NF* standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the *USP* or *NF* standards, tests, or assays requiring their use are announced via *Supplements* or *Interim Revision Announcements.*

The *Assay* portion of the monograph will become official when the new lot of USP Vinorelbine Tartrate RS becomes available. We anticipate that this will occur on or around September 1, 2005. USP will announce the availability of the new lot and the new official date of the *Assay* in a *Supplement* or an *Interim Revision Announcement.*

The valid use date of USP Vinorelbine Tartrate RS Lot F0C243 will expire at the time that the new lot becomes available. At that time, USP will provide all customers with vials of the new lot in exchange for unopened vials from Lot F0C243.

If you have any questions or concerns, please contact Lawrence Evans III, Ph.D., Scientist, DSD and scientific liaison to the Pharmaceutical Analysis 6 Expert Committee/ Monograph Development: Ophthalmology, Oncology and Dermatology (301-816-8389 or le@usp.org).

Vinorelbine Injection

Change to read:

•**Assay—**

Phosphate buffer, Mobile phase, and *System suitability solution*—Proceed as directed in the test for *Related compounds* under *Vinorelbine Tartrate*.

Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about 0.10 mg of vinorelbine (base) per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode-array detector and a 3.9-mm × 15-cm column that contains packing L1. The column temperature is maintained at 40°. 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 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A; and the relative retention, α, between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.

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 vinorelbine peaks, using a diode-array detector. Calculate the quantity, in mg, of vinorelbine ($C_{45}H_{54}N_4O_8$) in each mL of the Injection taken by the formula:

$$C(L/D)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation; L* is the labeled quantity, in mg, of vinorelbine in each mL of Injection taken; D is the concentration, in mg per mL, of vinorelbine in the *Assay preparation;* and r_U and r_S are the peak responses at 267 nm obtained from the *Assay preparation* and the *Standard preparation,* respectively.

(Postponed indefinitely)●5

NOTICE OF POSTPONEMENT

USP General Chapter *Injections* ⟨1⟩, *Printing on Ferrules and Cap Overseals*

USP has **postponed indefinitely** the official date of *Printing on Ferrules and Cap Overseals* that is published in *USP 28–NF 23* on page 2203. This section was originally slated to become official on October 5, 2005. The postponement is to allow for a revision for printing on ferrules and cap overseals that was approved by the Parenteral Products—Industrial, Nomenclature and Labeling, and Safe Medication Use Expert Committees to be published under *In-Process Revision* in this *Pharmacopeial Forum.* The Parenteral Products—Industrial Expert Committee will review comments concerning this revision. USP proposes that this General Chapter revision go forward to official text once public comments have been considered.

Should you have any questions, please contact James Kelly, Ph.D., Scientist, General Policies and Requirements Division and liaison to the Parenteral Products—Industrial Expert Committee (301-816-8167 or jwk@usp.org).

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

(Official October 1, 2005)

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. The contents of up to five 1- or 2-mL containers may be pooled for the measurement, provided that a separate dry syringe assembly is used for each container. The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

•(Postponed indefinitely)•S

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

MONOGRAPHS (USP)

Etodolac Extended-Release Tablets

Add the following:

•**Labeling**—When more than one *Dissolution* test is provided, the labeling states the *Dissolution* test used only if *Test 1* is not used.•5

Change to read:

•**Dissolution** ⟨711⟩—

TEST 1—•5

Medium: 0.05 M phosphate buffer, pH 7.4; 1000 mL.

Apparatus 2: 75 rpm, with USP sinker.

Times: 3, 6, 10, and 16 hours.

Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 279 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Etodolac RS in the same *Medium.* Use *Medium* as the blank.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to •*Acceptance Table 2.*•5

Time (hours)	Amount dissolved
3	between 15% and 40%
6	between 35% and 70%
10	between 60% and 95%
16	not less than 80%

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.05 M phosphate buffer, pH 7.5; 1000 mL.

Apparatus 2: 100 rpm.

Times: 2, 4, 8, and 14 hours.

Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by comparing the difference between the absorbances of the filtered portions of the solution under test determined at 278 nm and 245 nm with the difference between the absorbances of a Standard solution having a known concentration of USP Etodolac RS in the same *Medium* determined at the same wavelengths. Use *Medium* as the blank, and use a 0.05-cm silica cell.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 35%
4	between 30% and 55%
8	between 60% and 90%
14	not less than 85%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Medium: 0.05 M phosphate buffer, pH 6.8; 1000 mL.

Apparatus 2: 75 rpm.

Times: 2, 4, 8, and 14 hours.

Procedure—Determine the amount of $C_{17}H_{21}NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm on portions of the solution under test passed through a 10-µm polyethylene filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Etodolac RS in the same *Medium.* Use *Medium* as the blank, and use a 0.05-cm silica cell.

Tolerances—The percentages of the labeled amount of $C_{17}H_{21}NO_3$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 30%
4	between 30% and 50%
8	between 55% and 75%
14	not less than 80%

•5

Oxandrolone Tablets

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.•5

Change to read:

■**Dissolution** ⟨711⟩—

•TEST 1—•5

Medium: a solution of water and isopropanol (7 : 3); 500 mL.

Apparatus 2: 100 rpm.

Time: 60 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Internal standard solution—Dissolve accurately weighed quantities of 17α-methyltestosterone, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.2 mg per mL (for tablets with a 2.5-mg label claim) and about 0.8 mg per mL (for tablets with a 10-mg label claim).

Standard solution—Dissolve an accurately weighed quantity of USP Oxandrolone RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 1 mg per mL.

Working standard solution—Combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polytef filter. Transfer 20 mL of the filtrate to a separatory funnel, add 400 µL of the *Internal standard solution,* 40 mL of a 10% potassium chloride solution, and 8 mL of chloroform. In separate separatory funnels, prepare an extraction blank and an internal standard blank in a similar manner using 20 mL of filtered *Medium* in place of the solution under test and excluding the *Internal standard solution* from the extraction blank. Shake each funnel, and allow the layers to separate. Collect the lower chloroform layer. Repeat the extraction procedure one more time. Evaporate the solvents under a stream of nitrogen at 45° until just dry. Reconstitute the dried residue with 2 mL of acetonitrile (for tablets with a 2.5-mg label claim) or with 8 mL of acetonitrile (for tablets with a 10-mg label claim), and sonicate for 10 minutes.

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 0.5-µm phase G27. The carrier gas is helium, flowing at a rate of about 16.8 mL per minute. The injection port and detector temperatures are

maintained at 190° and 320°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is increased at a rate of 25° per minute to 280°, and maintained at 280° for 3 minutes. Then the column temperature is increased at a rate of 10° per minute to 320°, and maintained at 320° for 3 minutes. Chromatograph the acetonitrile, the extraction blank, and the internal standard blank, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5. Make two injections of the *Working standard solution,* and record the peak responses. The average oxandrolone/*Internal standard solution* peak area percent comparison is between 98.0% and 102.0%. The resolution, *R,* between the oxandrolone peak and the nearest eluting peak is equal to or greater than 1.5.

Procedure—Separately inject equal volumes (0.5 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{19}H_{30}O_3$ released by the formula:

$$\frac{C_S \times \text{sample ratio} \times V_{UF} \times 500 \times 100}{\text{Standard ratio} \times V_{UI} \times LC}$$

in which C_S is the concentration, in mg per mL, of oxandrolone in the *Standard solution;* sample ratio is the area ratio of oxandrolone to 17α-methyltestosterone in the sample injection for each *Test solution;* V_{UF} is the final volume, in mL, of the sample after reconstitution of the dry residue; 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; standard ratio is the mean area ratio of oxandrolone to 17α-methyltestosterone in all injections of the *Working standard solution;* V_{UI} is the initial sample volume, in mL, used in the extraction; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of oxandrolone ($C_{19}H_{30}O_3$) is dissolved in 60 minutes.■2S (*USP28*)

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 1% polysorbate 80 in water; 500 mL, deaerated.

Apparatus 2: 100 rpm.

Time: 120 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 20 mg of USP Oxandrolone RS, accurately weighed, to a 200-mL volumetric flask. Add about 20 mL of acetonitrile, and sonicate to dissolve. Dilute with *Medium* to volume, and mix.

Working standard solution—Quantitatively dilute the *Standard stock solution* with *Medium* to obtain a solution having a final concentration of about 5 µg per mL for Tablets with a label claim of 2.5 mg, or a final concentration of about 20 µg per mL for Tablets with a label claim of 10 mg.

Test solution—Withdraw about 10 mL of the solution under test from the vessel. Centrifuge in a glass tube at 2000 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a reflective index detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{19}H_{30}O_3$ released by the formula:

$$\frac{r_U \times C_S \times D \times 500 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* *D* is the dilution factor of the *Test solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim in mg.

Tolerances—Not less than 65% *(Q)* of the labeled amount of $C_{19}H_{30}O_3$ is dissolved in 120 minutes.•5

Sodium Polystyrene Sulfonate Suspension

Change to read:

» Sodium Polystyrene Sulfonate Suspension is a suspension of Sodium Polystyrene Sulfonate in an aqueous vehicle •that may contain suitable suspending or stabilizing agents. It•5 exchanges not less than 110 mg and not more than 135 mg of potassium for each g of the labeled amount of sodium polystyrene sulfonate.

Delete the following:

•**Labeling—**Label it to state the quantity of sorbitol in a given volume of Suspension.•5

Delete the following:

•**USP Reference standards** ⟨11⟩—*USP Sorbitol RS.*•5

Delete the following:

•**Assay for sorbitol—**

Mobile phase, Resolution solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Sorbitol* (see *NF* monograph).

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Assay preparation—Dilute an accurately measured volume of Suspension, freshly mixed and free from air bubbles, quantitatively with water to obtain a solution containing about 4.8 mg of sorbitol per mL. Filter, and use the filtrate as the *Assay preparation*.

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 responses for the major peaks. Proceed as directed for *Procedure* in the *Assay* under *Sorbitol* (see *NF* monograph). Calculate the quantity, in g, of $C_6H_{14}O_6$, in each mL of the Suspension taken by the formula:

$$(L / D)(C)(r_U / r_S),$$

in which L is the labeled quantity, in g, of sorbitol in each mL of Suspension; D is the quantity, in mg, of sorbitol in each mL of the *Assay preparation* based on the labeled quantity and the extent of dilution; C is the concentration, in mg per mL, of *USP Sorbitol 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.●5

ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
123	*Aminocaproic Acid*	*Assay*	Lines 5 and 6 under *Procedure:* Change "Calculate the quantity, in mg," to: Calculate the quantity, in g,
208	*Azithromycin*	*Labeling*	Line 5: Change "($C_{28}H_{72}N_2O_{12}$)" to: ($C_{38}H_{72}N_2O_{12}$)
884	*Gadoteridol Injection*	*Limit of free gadolinium (III)*	Line 7 under *Procedure:* Change ''500(157.25/334.38)(C/VP)($r_U r_S$)" to: 500(157.25/334.38)(C/VP)(r_U / r_S)
1235	*Methadone Hydrochloride Oral Solution*	*Assay*	Line 12 under *Procedure:* Change "R_U and R_S are the peak response ratios of the internal standard and methadone hydrochloride peaks" to: R_U and R_S are the peak response ratios of the methadone hydrochloride to the internal standard peaks
2578	⟨1047⟩ *Biotechnology-Derived Articles—Tests*	*Table 1*	Change ''Pepsin (EC 3.4.23.122)" to: Pepsin (EC 3.4.23.1) Change "(EC 23.4.21.19)" to: (EC 3.4.21.19) Change "(Clostripan)" to: (Clostripain)
Supplement 2			
3505	*Metolazone Tablets*	*Assay*	Line 6 under *Chromatographic system:* Change "replicate injections is not less than 2.0%" to: replicate injections is not more than 2.0%
3632	*Reagents, Indicators, and Solutions*	*Volumetric Solutions*	Under Iodine, Hundredth-Normal (0.01 N): Change denominator from "25" to: 100

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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24*; and

■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*, ■2S (*USP 28*) indicates that the proposed revision is slated for the *Second Supplement to USP 28*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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.

MONOGRAPHS (USP)

BRIEFING

Albumin Human, *USP 28* page 57 and page 992 of *PF* 29(4) [July–Aug. 2003]. On the basis of comments received, it is proposed to use the atomic absorption spectroscopic method instead of the flame photometric method for the estimation of *Potassium content* and *Sodium content.* A new section on *Incubation* of the final product has also been added.

(BBP: R. Tirumalai) RTS—42998-1

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)*~~

■» Albumin Human is a sterile, nonpyrogenic preparation of serum albumin. The source material of Albumin (Human) shall be plasma derived from Whole Blood from healthy human donors. The source material is tested for syphilis, hepatitis B virus, human T-cell virus (HTLV) type I and type II using FDA licensed commercially available test kits. In addition, the source material must also be tested for hepatitis C and HIV using FDA approved nucleic acid assays, and other disease-causative agents that may not be 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 is obtained. ■2S *(USP29)*

~~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)*~~

■Albumin Human is manufactured 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 (or as determined by a method that has been approved for each manufacturer). ■2S *(USP29)*

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 sodi-~~

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~~um 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.~~

■■2S (*USP29*)

■It contains no added antimicrobial agent. Either 0.08 ± 0.016 millimole sodium caprylate, or 0.08 ± 0.016 millimole sodium acetyltryptophanate and 0.08 ± 0.016 millimole sodium caprylate per gram of protein may be present as a stabilizer(s).■2S (*USP29*)

Change to read:

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

■■2S (*USP29*)
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)if labeling recommends storage between 2° and 10°; not later than 3 years after issue from manufacturer's cold storage (5°, 3 years)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°.~~

■The expiration date is not later than 5 years after the date of final sterile filtration of a uniform pool of the bulk solution.■2S (*USP29*)

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, placental 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.■2S (*USP29*)

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Albumin Human RS. USP Endotoxin RS.*■2S (*USP29*)

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

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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.■2S (*USP29*)

Add the following:

■**Bacterial endotoxins** ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mL.■2S (*USP29*)

Add the following:

■**Safety**—It meets the requirements when tested as directed for *Safety Tests—Biologicals* under *Biological Reactivity Tests, In Vivo* ⟨88⟩■2S (*USP29*)

Add the following:

■**Sterility** ⟨71⟩—It meets the requirements.■2S (*USP29*)

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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.■2S (*USP29*)

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.■2S (*USP29*)

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.■2S (*USP29*)

Add the following:

■**Incubation—**All final containers of Albumin Human shall be incubated at 20° to 35° for at least 14 days following the heat treatment. At the end of this incubation period, each final container shall be examined and all containers showing any indication of turbidity or microbial contamination shall not be issued. The contents of turbid final containers shall be examined microscopically and tested for sterility. If growth occurs, organisms shall be identified as to genus, and the material from such containers shall not be used for further manufacturing.■2S (*USP29*)

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. Pass the solution through 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.■2S (*USP29*)

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.

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

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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.■2S (*USP29*)

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.■2S (*USP29*)

Add the following:

■**Potassium content**—

Standard solutions 1, 2, 3, 4, 5, 6, and *7*—~~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.~~ Prepare seven standard solutions containing 0, 0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 µg of potassium, in the form of the chloride, per mL, respectively, in cesium chloride diluent.

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.~~ Dilute the albumin samples to approximately 5% using water and further dilute the 5% protein solutions 5 mL to 50 mL using cesium chloride diluent.

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.~~ Set a suitable atomic absorption spectrophotometer capable of analyzing in emission mode to a wavelength of 766.5 nm. Operate the atomic emission spectrometer in accordance with the manufacturer's instructions. Introduce a blank solution (using cesium chloride diluent) into the atomic generator, and adjust the instrument reading to zero. Determinations are made by comparison with reference solutions with known concentrations. Use the 1 µg/mL standard as the check standard. The result must be 1.0 ± 0.05 µg/mL. If outside this range recalibrate the instrument. If the sample solution emission exceeds that of the highest standard, dilute the sample using cesium chloride diluent. Read the emission of *Standard solutions 2–7*. Plot the observed emission of *Standard solutions 2–7* against their respective potassium concentrations. From the standard curve calculate the potassium content in µg per mL of the *Test solution*. Convert the value to obtain potassium concentration in mEq per L in the sample. Albumin Human contains not more than 2 mEq/L of potassium.■2S (*USP29*)

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Add the following:

■**Sodium content**—

Standard solutions 1, 2, 3, 4,5,6, and *7*—~~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.~~ Prepare seven standard solutions containing 0, 0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 µg of sodium, in the form of the chloride, per mL, respectively, in cesium chloride diluent.

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.~~ Dilute the albumin samples to approximately 5% using water, and further dilute the 5% protein solutions 5 mL to 50 mL using cesium chloride diluent.

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 dilution 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.~~ Set a suitable atomic absorption spectrophotometer capable of analyzing in emission mode to a wavelength of 589 nm. Other details are as described under *Potassium content*. From the standard curve calculate the sodium content in µg per mL of the *Test solution*. Convert the value to obtain the sodium concentration in mEq per L in the sample. Albumin Human contains between 130 to 160 mEq/L of sodium.■2S (*USP29*)

BRIEFING

Alendronate Sodium, *USP 28* page 63. It is proposed to revise the *Packaging and storage* statement to indicate storage at room temperature rather than restricting the storage temperature to between 15° and 30°.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—42722-1

Change to read:

Packaging and storage—Preserve in well-closed containers. ~~Store between 15° and 30°.~~

■Store at room temperature.■2S (*USP29*)

BRIEFING

Amantadine Hydrochloride, *USP 28* page 111. It is proposed to revise the *Chromatographic system* in the test for *Chromatographic purity* to identify the peak as amantadine (the base) rather than amantadine hydrochloride (the salt). The base is the chemical entity being chromatographed in this procedure.

(PA7b: B. Davani) RTS—42338-1

Change to read:

Chromatographic purity—

Internal standard solution—Transfer about 500 mg of adamantane, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with dichloromethane to volume, and mix.

Test solution—Transfer about 1.0 g of Amantadine Hydrochloride, accurately weighed, to a separator. Add 20 mL of 5.0 N sodium hydroxide and 18 mL of dichloromethane, and shake for 10 minutes. Remove the water layer, dry the organic layer by swirling with anhydrous sodium sulfate, and allow to stand for a few minutes to ensure that all remaining water has been removed. Filter, collect the filtrate in a 20-mL volumetric flask, add 0.2 mL of *Internal standard solution,* and dilute with dichloromethane to volume.

Standard solution—Transfer about 10 mg of USP Amantadine Hydrochloride RS, accurately weighed, to a separator. Add 20 mL of 5.0 N sodium hydroxide and 18 mL of dichloromethane, and shake for 10 minutes. Remove the water layer, dry the organic layer by swirling with anhydrous sodium sulfate, and allow to stand for a few minutes to ensure that all remaining water has been removed. Filter, collect the filtrate in a 20-mL volumetric flask, add 0.2 mL of *Internal standard solution,* and dilute with dichloromethane to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m fused-silica column coated with 1.0-µm G27 stationary phase. The carrier gas is helium, flowing at a rate of about 4 mL per minute, and the split flow is about 200 mL per minute with a split flow ratio of 50 : 1. Initially, the temperature of the column is equilibrated at 70° for 5 minutes, then the temperature is increased linearly at a rate of 10° per minute to 250°, and maintained at 250° for at least 17 minutes. The injection port temperature is maintained at 220°, and the detector temperature is maintained at 300°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for adamantane and 1.0 for amantadine; ~~hydrochloride~~

■ ■2S (*USP29*)
the resolution, *R,* between adamantane and amantadine ~~hydrochloride~~

■ ■2S (*USP29*)
is not less than 20; and the relative standard deviation for replicate injections determined from the peak response ratios of amantadine to adamantane is not more than 5.0%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Amantadine Hydrochloride taken by the formula:

$$100(R_i/R_S)(W_S/W_U)$$

in which R_i is the peak response ratio of each impurity to adamantane obtained from the *Test solution;* R_S is the peak response ratio of amantadine to adamantane obtained from the *Standard solution;* W_S is the weight, in mg, of USP Amantadine Hydrochloride RS taken to prepare the *Standard solution;* and W_U is the weight, in mg, of Amantadine Hydrochloride taken to prepare the *Test solution*: not more than 0.3% of any individual impurity is found; and not more than 1.0% of total impurities is found.

BRIEFING

Aspartic Acid, *USP 28* page 179 and page 3212 of the *First Supplement.* In the test for *Chloride,* it is proposed to increase the volume of nitric acid used to improve the solubility of the sample.

(DSN: L. Evans) RTS—42190-1

Change to read:

Chloride ⟨221⟩**—**Dissolve 0.7 g in ~~3~~

■10 ■2S (*USP29*)
mL of diluted nitric acid, and dilute with water to make 15 mL: the solution shows no more chloride than corresponds to 0.20 mL of 0.020 N hydrochloric acid (0.02%).

BRIEFING

Atenolol, *USP 28* page 193. It is proposed to revise the formula in the *Assay.*

(PA5: A. Wilk) RTS—42824-1

Change to read:

Assay—

Mobile phase—Dissolve 1.1 g of sodium 1-heptanesulfonate and 0.71 g of anhydrous dibasic sodium phosphate in 700 mL of water. Add 2 mL of dibutylamine, and adjust with 0.8 M phosphoric acid to a pH of 3.0. Add 300 mL of methanol, mix, and pass through a filter having a 0.5-µm or finer porosity. Degas this solution before use. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Atenolol RS in *Mobile phase* to obtain a solution having a known concentration of about 0.01 mg per mL.

Assay preparation—Transfer about 100 mg of Atenolol, accurately weighed, to a 100-mL volumetric flask, add 50 mL of *Mobile phase,* and sonicate for about 5 minutes. 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. Transfer 5.0 mL of this solution to a second 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 226-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 0.6 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:*

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the column efficiency is not less than 5000 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 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 $C_{14}H_{22}N_2O_3$ in the portion of Atenolol taken by the formula:

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

■$10{,}000C(r_U/r_S)$■2S *(USP29)*

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

BRIEFING

Bromocriptine Mesylate, *USP 28* page 282. On the basis of comments received and submitted data, it is proposed to revise the impurities specification in the test for *Chromatographic purity.*

(PA1: C. Anthony) RTS—42995-1

Change to read:

Chromatographic purity—

Citrate buffer—Prepare a 0.1 N citric acid solution, adjust with hydrochloric acid to a pH of 2.0, and mix.

Diluting solution—Prepare a mixture of methanol and *Citrate buffer* (1 : 1).

Solution A—Mix 57 mL of 0.01 M phosphate buffer having a pH of 7.0 and 43 mL of acetonitrile.

Solution B—Mix 40 mL of 0.01 M phosphate buffer having a pH of 7.0 and 60 mL of 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 α-ergocryptine and Bromocriptine Mesylate in *Diluting solution* to obtain a solution containing about 2.0 mg of each per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Bromocriptine Mesylate RS in methanol, dilute quantitatively with an equal volume of *Citrate buffer*, and dilute quantitatively, and stepwise if necessary, with *Diluting solution* to obtain a solution having a known concentration of about 4.6 µg per mL.

Test solution—Transfer about 46 mg of Bromocriptine Mesylate, accurately weighed, to a 10-mL volumetric flask, dissolve in 5.0 mL of methanol, dilute with *Citrate buffer* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 300-nm detector and a 4.6-mm × 15-cm column that contains 3-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	100	0	equilibration
0–18	100	0	isocratic
18–30	100→0	0→100	linear gradient
30–40	0	100	isocratic
40–41	0→100	100→0	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.46 for α-ergocryptine and 1.0 for bromocriptine mesylate; the resolution, *R,* between α-ergocryptine and bromocriptine mesylate is not less than 15; and the tailing factor is not more than 1.5. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the retention time for the bromocriptine mesylate peak is between 17 and 20 minutes; and the relative standard deviation for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Bromocriptine Mesylate taken by the formula:

$$1000F(C/W)(r_i/r_S)$$

in which F, the relative response factor, is equal to 0.7 for any peaks eluting at a relative retention time of about 0.9 or less, and is equal to 1.0 for all other peaks; C is the concentration, in mg per mL, of USP Bromocriptine Mesylate RS in the *Standard solution;* W is the weight, in mg, of Bromocriptine Mesylate 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 bromocriptine obtained from the *Standard solution:*

■not more than 0.4% bromcriptinin is found;■2S *(USP29)*
not more than 0.1% of any individual impurity is found; and not more than ~~0.5%~~

■1.0%■2S *(USP29)*
of total impurities is found.

BRIEFING

Butorphanol Tartrate Nasal Solution. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analysis performed with the Symmetry brand of L11 column. The typical retention time is about 8.7 minutes for butorphanol tartrate.

(PA2: C. Anthony) RTS—42160-1

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Add the following:

■Butorphanol Tartrate Nasal Solution

» Butorphanol Tartrate Nasal Solution is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of butorphanol tartrate, ($C_{21}H_{29}NO_2 \cdot C_4H_6O_6$)

Packaging and storage—Preserve in tight containers at controlled room temperature. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—***USP Butorphanol Tartrate 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: *Thin-layer chromatographic identification test* ⟨201⟩—

Test solution—Prepare one sample composite solution by pooling the contents of three packages into a suitable vessel. Transfer 1.0 mL of pooled sample to a 10-mL volumetric flask, and dilute with methanol to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in methanol to obtain a solution having a known concentration of about 1.0 mg per mL.

Developing solvent system—Prepare a mixture of chloroform, methanol, benzene, and ammonium hydroxide (17 : 5 : 4 : 1). Mix thoroughly. *[Caution—Prepare in a hood while wearing appropriate safety gloves, lab coat, and protective eyewear.]*

Spray reagent—Prepare a 1 in 10 solution of chloroplatinic acid in water. To 0.5 mL of this solution, add 33 mL of water and 1 g of potassium iodide. Prepare fresh daily.

Procedure—Proceed as directed in the chapter, except to spray the plate with the *Spray reagent*. The typical R_F value is about 0.7 for butorphanol tartrate.

Osmolality ⟨785⟩**:** between 252 and 292 mOsmol per kg.

Microbial limits ⟨61⟩**—**The total aerobic count is not more than 100 cfu per mL, and the total combined molds and yeasts count is not more than 100 cfu per mL. It meets the requirements of the tests for absence of *Coliforms, Staphylococcus aureus,* and *Pseudomonas aeruginosa*.

pH ⟨791⟩**:** between 4.0 and 6.0.

Delivered dose uniformity over the entire contents: meets the requirements for *Metered-Dose Inhalers* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.

Related compounds—

Phosphate buffer (0.025 M)—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of phosphate buffer, acetonitrile, and triethylamine (85 : 15 : 5). Thoroughly mix. Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in water, and quantitatively dilute in water as necessary to obtain a solution having a known concentration of about 0.005 mg per mL.

Sensitivity solution—Transfer 2.5 mL of the *Standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix. Do not filter.

Test solution—Prepare a sample composite solution by pooling a minimum of four containers into a suitable glass vessel. Transfer the equivalent of 50 mg of butorphanol tartrate into a 50-mL volumetric flask. Dilute with water to volume, and mix. Do not filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6- × 250-mm column that contains 5-µm packing L11, and a 4.6- × 10-mm guard column packed with 5-µm packing L11. The column temperature is maintained at 40°. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six replicate injections is not more than 10.0%. Chromatograph the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the peak height for butorphanol tartrate is greater than or equal to three times the base line noise.

Procedure—Separately inject equal volumes (about 60 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the butorphanol tartrate peak in the *Standard solution* and all known and unknown related compounds in the *Test solution*. The chromatographic run time is about 40 minutes. Calculate the percentage of each related compound (see *Table 1*) and unknown impurity in the sample of Nasal Solution taken by the formula:

$$5000(C/VLA)(r_i / r_S)$$

in which C is the concentration, in mg per mL, of USP Butorphanol Tartrate RS in the *Standard solution; V* is the volume of sample taken; *LA* is the labeled amount, in mg per mL, of butorphanol tartrate in the sample; r_i is the peak response of the known or unknown related compound in the *Test solution;* and r_S is the peak response of butorphanol tartrate in the *Standard solution:* the impurities meet the requirements specified below.

Table 1

Compounds	Relative Retention Time	Limit (%)
3,14-Dihydroxymorphinan	0.3	0.3
Δ6-Butorphanol	0.7	0.5
Butorphanol tartrate	1.0	—
Unknown impurity	—	0.3
Total impurities	—	1.0

Assay—

Phosphate buffer (0.025 M)—Transfer 3.4 g of monobasic potassium phosphate into a 1000 mL volumetric flask. Dilute with water to volume, and filter. Mix, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of phosphate buffer, acetonitrile, and triethylamine (85 : 15 : 2). Thoroughly mix. Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in *Mobile phase* to obtain a solution having a known concentration of 0.2 mg per mL. Mix, and filter discarding the first 2 mL of the filtrate. The *Standard preparation* is stable for at least 108 hours.

Assay preparation—Prepare a sample composite solution by pooling a minimum of four containers into a suitable glass vessel. Transfer the equivalent of 20 mg of butorpha-

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nol tartrate into a 100-mL volumentric flask. Dilute with *Mobile phase* to volume, mix, and filter discarding the first 2 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector, a 4.6- × 250-mm column that contains 5-µm packing L11, and a 4.6- × 10-mm guard column that contains 5-µm packing L11. The column temperature is maintained at 30°. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the butorphanol tartrate peak is not more than 2.0; and the relative standard deviation for five 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 the chromatograph, record the chromatograms, and measure the responses for the butorphanol tartrate peak in the *Standard preparation* and the *Assay preparation*. Calculate the quantity, in mg, of butorphanol tartrate ($C_{21}H_{29}NO_2 \cdot C_4H_6O_6$) in the portion of the Nasal Solution taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Butorphanol Tartrate RS in the *Standard preparation;* and r_U and r_S are the peak responses of butorphanol tartrate in the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

BRIEFING

Carboxymethylcellulose Sodium, *USP 28* page 358. It is proposed to revise the sample preparation in the test for *Heavy metals* to align it with recent changes to USP general chapter *Heavy Metals* ⟨231⟩.

(EMC: J. Lane) RTS—42876-2

Change to read:

Heavy metals, *Method II* ⟨231⟩: ~~Determine as directed in the test for *Heavy metals* under *Methylcellulose,* using a 1.0-g specimen: the limit is 20 µg per g.~~

■0.002%, adding 1 mL of hydroxylamine hydrochloride solution (1 in 5) to the solution of the residue.■2S (*USP29*)

BRIEFING

Carboxymethylcellulose Sodium Paste, *USP 28* page 359. It is proposed to revise the sample preparation in the test for *Heavy metals* to align it with recent changes to USP general chapter *Heavy Metals* ⟨231⟩.

(EMC: J. Lane) RTS—42876-4

Change to read:

Heavy metals, *Method II* ⟨231⟩: ~~Determine as directed in the test for *Heavy metals* under *Methylcellulose,* using a 400-mg specimen: the limit is 0.005%.~~

■0.005%, using an 800-mg specimen and adding 1 mL of hydroxylamine hydrochloride solution (1 in 5) to the solution of the residue.■2S (*USP29*)

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BRIEFING

Clindamycin Hydrochloride Oral Solution, *USP 28* page 494. On the basis of data received, it is proposed to widen the acceptable range of pH from between 3.0 and 5.5 to between 2.5 and 6.0. Interested parties are invited to submit comments.

(PA7a: B. Gilbert) RTS—42518-1

Change to read:

pH ⟨791⟩: between ~~3.0 and 5.5.~~

■2.5 and 6.0.■2S (*USP29*)

BRIEFING

Cyanocobalamin, *USP 28* page 554. It is proposed to specify the type of cresol reagent used in the test for *Pseudo cyanocobalamin.*

(DSN: L. Evans) RTS—42708-1

Change to read:

Pseudo cyanocobalamin—Dissolve 1.0 mg in 20 mL of water contained in a small separator, add 5 mL of a mixture of equal volumes of carbon tetrachloride and ~~cresol~~

■*m*-cresol,■2S (*USP29*)
and shake well for about 1 minute. Allow to separate, draw off the lower layer into a second small separator, add 5 mL of 5 N sulfuric acid, shake well, and allow to separate completely (the complete separation of the layer may be facilitated by centrifuging): the separated upper layer is colorless or has no more color than a mixture of 0.15 mL of 0.10 N potassium permanganate and 250 mL of water.

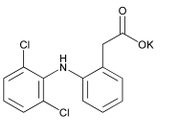
BRIEFING

Diclofenac Potassium. 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* are based on analyses performed with the Ultrasphere C8 brand of L7 column. Typical retention times are about 11.1 minutes for diclofenac potassium and about 6.8 minutes for diclofenac potassium related compound A.

(PA2: C. Anthony) RTS—39091-1

Add the following:

■Diclofenac Potassium



$C_{14}H_{10}Cl_2KNO_2$ 334.24

(1) Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monopotassium salt.

(2) Potassium [*o*-(2,6-dichloroanilino)phenyl]acetate [*15307-81-0*].

» Diclofenac Potassium contains not less than 99.0 percent and not more than 101.0 percent of $C_{14}H_{10}Cl_2KNO_2$, calculated on the dried basis.

Packaging and storage—Preserve in light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Diclofenac Potassium RS. USP Diclofenac Related Compound A RS.*

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Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 0.1 mg per mL.

Medium: methanol.

C: It meets the requirements of the flame test for *Potassium* ⟨191⟩.

pH ⟨791⟩**:** between 7.0 and 8.5, in a 1% aqueous solution.

Loss on drying ⟨731⟩**—**Dry it at 105° under vacuum for three hours: it loses not more than 0.5% of its weight.

Heavy metals, *Method II* ⟨231⟩**:** not more than 10 ppm.

Related compounds—

pH 2.5 Phosphate buffer—Mix equal volumes of 0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. If necessary, adjust with additional portions of the appropriate components to a pH of 2.5 ± 0.2.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *pH 2.5 Phosphate buffer* (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (70 : 30).

Standard solution—Prepare a solution of USP Diclofenac Related Compound A RS in methanol having a known concentration of about 0.25 mg per mL. Quantitatively dilute an accurately measured volume of this stock solution with *Diluent* to obtain a solution having a known concentration of about 1.5 µL per mL.

Resolution solution—Prepare a solution in *Diluent* containing 40 µg per mL of diethyl phthalate, 0.5 mg per mL of USP Diclofenac Potassium RS, and 22.5 µg per mL of USP Diclofenac Related Compound A RS.

Test solution—Transfer about 50 mg of Diclofenac Potassium, 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 × 25-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 0.5 for diethyl phthalate, 0.7 for diclofenac related compound A, and 1.0 for diclofenac potassium; and the resolution, *R,* between diethyl phthalate and diclofenac related compound A is not less than 4.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses. Calculate the percentage of diclofenac related compound A in the portion of Diclofenac Potassium taken by the formula:

$$10(C/W)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Diclofenac Related Compound A RS in the *Standard solution;* W is the quantity, in mg, of Diclofenac Potassium taken to prepare the *Test solution;* and r_U and r_S are the diclofenac related compound A peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of diclofenac related compound A is found. Calculate the percentage of each other impurity in the portion of Diclofenac Potassium taken by the formula:

$$10(C/W)(r_i/r_S)$$

in which r_i is the individual peak response of each impurity obtained from the *Test solution;* and the other terms are as

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defined above: not more than 0.1% of each individual impurity is found, and not more than 0.3% of total impurities is found.

Assay—

Procedure—Dissolve about 300 mg of Diclofenac Potassium, accurately weighed, in 50 mL of glacial acetic acid, and titrate with 0.1N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1N perchloric acid is equivalent to 33.424 mg of $C_{14}H_{10}Cl_2KNO_2$. ■2S (*USP29*)

BRIEFING

Diclofenac Potassium Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the Symmetry brand of L7 column. The typical retention time for diclofenac potassium is about 10.2 minutes.

(PA2: C. Anthony; BPC: M. Marques) RTS—39091-2; 39091-3

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Add the following:

■Diclofenac Potassium Tablets

» Diclofenac Potassium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{10}Cl_2KNO_2$.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Diclofenac Potassium RS. USP Diclofenac Related Compound A RS.*

Identification—

A: The retention time of the diclofenac peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation,* as obtained in the *Assay.*

B: It meets the requirements of the flame test for *Potassium* ⟨191⟩.

Dissolution ⟨711⟩—

Medium: simulated intestinal fluid (without enzyme); 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{14}H_{10}Cl_2NKO_2$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 276 nm on portions of the solution under test passed through a 0.45 µm filter, suitably diluted with *Medium,* if necessary, in comparison with a standard solution having a known concentration of USP Diclofenac Potassium RS in the same *Medium*. Calculate the percentage of diclofenac potassium $C_{14}H_{10}Cl_2NKO_2$ dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and LC is the Tablet label claim, in mg, of diclofenac potassium.

Tolerances —Not less than 80% (Q) of the labeled amount of $C_{14}H_{10}Cl_2KNO_2$ is dissolved in 60 minutes.

Loss on drying ⟨731⟩—Dry it at 105° ± 2° for 3 hours : it loses not more than 5.0% of its weight.

Limit of potassium—

Standard—Accurately transfer about 50.00 mg of potassium chloride into a fused quartz crucible.

Sample—Transfer not fewer than five diclofenac potassium 50-mg Tablets, accurately weighed, into a fused quartz crucible.

Blank—Prepare a dilution of 10% cesium chloride (1 in 50).

Test solutions—Place crucibles containing the *Standard, Sample,* and *Blank* in a muffle furnace at 550° for 8 hours to ash the contained material. Pipet 1.0 mL of concentrated hydrochloric acid and 1.0 mL of concentrated nitric acid into each cooled crucible. Heat each crucible on a hot plate to dissolve the residue. Ttransfer quantitatively, without filtering, the contents of each crucible to 100-mL volumetric flasks, and dilute with water to volume. Pipet 1.0 mL from each volumetric flask into separate 100-mL volumetric flasks, pipet 2.0 mL of 10% cesium chloride solution into each flask, and dilute with water to volume.

Procedure—Concomitantly determine the absorbances of the *Test solutions* and *Blank* at the potassium emission line at 766.5 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an air–acetylene flame. Plot the absorbances of the *Test solutions* versus their potassium content. Calculate the weight percentage of potassium in each Tablet: not less than 2.40% and not more than 2.94% is found; and not less than 90.0% and not more than 110.0% of the calculated theoretical amount of potassium is found.

Uniformity of dosage units: meets the requirements.

Related compounds—

pH 2.5 Phosphate buffer, Mobile phase, Diluent, Resolution solution, and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Diclofenac Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of diclofenac related compound A in the portion of Diclofenac Potassium Tablets taken by the formula:

$$10(C/A)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of diclofenac related compound A in the *Standard solution; A* is the quantity, in mg, of diclofenac potassium in the portion of Tablets taken to prepare the *Assay preparation,* as determined in the *Assay;* and r_U and r_S are the diclofenac related compound A peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of diclofenac related compound A is found. Calculate the percentage of each of the other impurities, other than diethyl phthalate, if

present, in the portion of Diclofenac Potassium Tablets taken by the formula:

$$10(C/A)(r_i / r_S)$$

in which r_i is the response of an individual impurity peak obtained from the *Test solution,* and the other terms are as defined above: not more than 0.1% of each individual impurity is found, and not more than 0.3% of total impurities is found.

Assay—

pH 2.5 Phosphate buffer—Mix equal volumes of 0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. If necessary, adjust with additional portions of the appropriate components to a pH of 2.5 ± 0.2.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *pH 2.5 Phosphate buffer* (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (70 : 30).

Standard preparation—Dissolve an accurately weighed quantity of USP Diclofenac Potassium RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 50 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 50 mg of diclofenac potassium, to a 100-mL volumetric flask. Add about 70 mL of *Diluent,* stir for 60 minutes, dilute with *Diluent* to volume, mix, and centrifuge.

Resolution solution—Prepare a solution in *Diluent* containing 40 µg per mL of diethyl phthalate, 0.5 mg per mL of USP Diclofenac Potassium RS, and 37.5 µg per mL of USP Diclofenac Potassium Related Compound A RS.

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 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between diethyl phthalate and diclofenac related compound A is not less than 2.5, and the resolution, *R,* between diclofenac related compound A and diclofenac is not less than 3.5. 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 diclofenac potassium ($C_{14}H_{10}Cl_2KNO_2$) in each Tablet taken by the formula:

$$(VC/20)(r_U / r_S)$$

in which V is the volume of the flask used to prepare the *Assay preparation*; C is the concentration, in mg per mL, of USP Diclofenac Potassium 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 (*USP29*)

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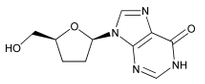
BRIEFING

Didanosine; Didanosine for Oral Solution; Didanosine Tablets. Because there are no existing *USP* monographs for this drug substance and dosage forms, new monographs based on submitted data are being proposed. For Didanosine and Didanosine for Oral Solution, the liquid chromatographic procedures in the *Related compounds* test and the *Assay* are based on analyses performed with the LC-18-DB (base deactivated; from Supelco) brand of L1 column. For Didanosine Tablets, the liquid chromatographic procedure used in the *Assay* and in the *Dissolution* and *Related compounds* tests is based on analyses performed with the LiChrospher 60 RP-Select B brand of L7 column.

(PA7b: B. Davani) RTS—42596-1

Add the following:

■Didanosine



$C_{10}H_{12}N_4O_3$ 236.23

2′,3′-Dideoxyinosine.

Dideoxyinosine [*69655-05-6*].

» Didanosine contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}N_4O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Didanosine RS. USP Didanosine Related Compound A RS. USP Didanosine Related Compound B RS. USP Didanosine System Suitability Mixture 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.*

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

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

Heavy metals, *Method II* ⟨231⟩**:** not more than 20 ppm.

Optical rotation ⟨781⟩**:** between –28° and –24°, anhydrous.

Test solution: 10 mg per mL solution in water.

Related compounds—

Ammonium acetate buffer solution 0.01 M—Prepare as directed in the *Assay.*

Solution A—Prepare a filtered and degassed mixture of *Ammonium acetate buffer solution 0.01 M* and acetonitrile (19 : 1).

Solution B—Prepare a filtered and degassed mixture of *Ammonium acetate buffer solution 0.01 M* and acetonitrile (3 : 1).

Diluent—Adjust the pH of *Ammonium acetate buffer solution 0.01M* with sodium hydroxide to 9, and mix. Prepare a degassed mixture of *Ammonium acetate solution 0.01 M* and acetonitrile (19 : 1).

Standard stock solution A—Dissolve an accurately weighed quantity of USP Didanosine Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.05 mg per mL.

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Standard stock solution B—Dissolve an accurately weighed quantity of USP Didanosine RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.025 mg per mL.

Standard stock solution C—Dissolve an accurately weighed quantity of USP Didanosine Related Compound B RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.025 mg per mL.

Standard solution—Transfer 5.0 mL of *Standard stock solution A*, 3.0 mL of *Standard stock solution B,* and 3.0 mL of *Standard stock solution C* into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

System suitability solution—Dissolve an accurately weighed quantity of USP Didanosine System Suitability Mixture RS in *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.

Test solution—Transfer about 50 mg of Didanosine, 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 25-cm × 4.6-mm column containing 5-µm diameter packing L1. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–15	100	0	isocratic
15–20	100→0	0→100	linear gradient
20–30	0	100	isocratic
30–35	0→100	100→0	linear gradient
35–45	100	0	equilibrium

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* didanosine elutes between 6 and 7.5 minutes; the relative retention times are about 1.0 for didanosine, 0.28 for didanosine related compound A, and 2.11 for didanosine related compound B; and the relative standard deviation for replicate injections determined on the didanosine related compound A peak is not more than 2.0%. [NOTE—5′-Deoxydideoxyadenosine, a potential impurity not added to the solution, elutes at a relative retention time of 3.1 minutes.] Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.0 for didanosine, 0.39 for inosine, 0.45 for 2′-deoxyinosine, 0.51 for 3′-deoxyinosine, 0.59 for 2′,3′-anhydroinosine, and 0.81 for dideoxydidehydroinosine; the resolution, *R,* between didanosine and dideoxydidehydroinosine is not less than 3.0; and the column efficiency determined on the dideoxydidehydroinosine peak is not less than 6000 theoretical plates.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for 30 minutes, and measure all the peak responses. Calculate the percentage of didanosine related compound A, 5′-deoxydideoxyadenosine, and each other impurity in the portion of Didanosine taken by the formula:

$$10{,}000(C/W(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Didanosine RS or USP Didanosine Related Compound A RS in the *Standard solution; W* is the weight, in mg, of the sample; r_i is the peak response of the *Test solution;* and r_S is the peak response of USP Didanosine RS or USP Didanosine Related Compound A RS in the *Standard solution.* Use the peak response of Didanosine in the *Standard solution*

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to calculate other individual impurities: not more than 0.5% of didanosine related compound A is found; not more than 0.2% of each specified impurity at the relative retention times of 0.39, 0.45, 0.51, 0.59, 0.81, 2.1, and 3.1 is found; not more than 0.1% of each other impurity is found; and not more than 1.0% of total impurities is found.

Assay—

Ammonium acetate buffer solution 0.01M—Dissolve 1.54 g of ammonium acetate in a 2000-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Ammonium acetate buffer solution 0.01 M* and acetonitrile (21 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution containing 0.1 mg per mL.

Assay preparation—Accurately weigh 50 mg of Didanosine, and place in a 500-mL volumetric flask. Dissolve in and dilute with water to volume. Mix the sample for 1 hour to dissolve completely before use.

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 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention time of didanosine is between 7 and 11 minutes, the column efficiency is not less than 6000 theoretical plates, 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 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 $C_{10}H_{12}N_4O_3$ in the portion of Didanosine taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Didanosine 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 (*USP29*)

BRIEFING

Didanosine for Oral Solution—See briefing under *Didanosine.*

(PA7b: B. Davani) RTS—42596-3

Add the following:

■Didanosine for Oral Solution

» Didanosine for Oral Solution, when reconstituted as directed in the labeling, yields a 10 mg per mL solution that contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$).

Packaging and storage—Preserve in tight containers, and store at a temperature between 15° and 30°.

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Labeling—The label contains directions for constitution of the powder and states the equivalent amount of $C_{10}H_{12}N_4O_3$ in a given volume of Oral Solution obtained after constitution.

USP Reference standards ⟨11⟩—*USP Didanosine RS*. *USP Didanosine 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.*

Water, *Method Ia* ⟨921⟩**:** not more than 3%.

Deliverable volume ⟨698⟩**:** meets the requirements.

Related compounds—

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

Standard solution—Dissolve an accurately weighed quantity of USP Didanosine Related Compound A RS in water to obtain a solution containing 5 µg per mL. Make stepwise dilutions if necessary. [NOTE—Use this solution within 48 hours of preparation.]

Test solution—Transfer the contents of 1 container of Didanosine for Oral Solution to a suitable volumetric flask, and dissolve in water to obtain a solution having a concentration of approximately 4 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Diluted test solution—Dilute the *Test solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of about 0.1 mg per mL.

Calculate the percentage of didanosine related compound A (hypoxanthine) in the Didanosine for Oral Solution as compared to the didanosine label claim by the formula:

$$[100(C/1000)(r_U/r_S)VD]/L$$

in which 100 is the conversion factor to percent; C is the concentration of didanosine related compound A in the *Standard solution,* in µg per mL; 1000 is the conversion factor (µg to mg); r_U and r_S are the peak responses of didanosine related compound A in the *Diluted test solution* and the *Standard solution,* respectively; V is the volume, in mL, of Didanosine for Oral Solution used to prepare the *Test solution; D* is the dilution factor of the *Diluted test solution;* and L is the didanosine label claim expressed in mg: not more than 1% is found.

Assay—

0.01 M Ammonium acetate buffer solution—Dissolve 1.54 g of ammonium acetate into a 2000-mL volumetric flask, dilute with water to volume, mix, and pass through a 0.45-µm filter.

Mobile phase—Prepare a filtered degassed mixture of *0.01 M Ammonium acetate buffer solution* and acetonitrile (24 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution containing 0.1 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Assay preparation—Transfer the contents of 1 bottle of Didanosine for Oral Solution to a suitable volumetric flask and dilute stepwise, if necessary, to obtain a solution in water of about 0.1 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector, a 4-mm × 25-cm analytical column containing packing

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L1, and a 4.6- × 20-mm guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for didanosine is between 7 and 11 minutes; the column efficiency is not less than 6000 theoretical plates; and the relative standard deviation 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. Calculate the quantity, in mg, of didanosine ($C_{10}H_{12}N_4O_3$) in the portion of Didanosine for Oral Solution taken by the formula:

$$(C)(D)r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Didanosine RS in the *Standard preparation; D* is the volume, in mL, of Didanosine for Oral Solution used to prepare the *Assay preparation* multiplied by the dilution factor of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP29)*

BRIEFING

Didanosine Tablets—See briefing under *Didanosine.*

(PA7b: B. Davani) RTS—42596-2

Add the following:

■Didanosine Tablets

» Didanosine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$).

Packaging and storage—Preserve in tight containers, and store between 15° and 30°.

Labeling—Label chewable Tablets to indicate that they are to be chewed before swallowing or dispersed in liquid before administration.

USP Reference standards ⟨11⟩—*USP Didanosine RS. USP Didanosine Related Compound A RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent—Merck silica gel 60 with fluorescent indicator, or equivalent.

Test solution—Place 1 Tablet in sufficient methanol to make a 1 mg per mL solution. Stir to dissolve, and pass through a 0.45-µm filter.

Standard solution—Transfer 10 mg of USP Didanosine RS into a 10-mL volumetric flask. Dissolve in and dilute with methanol to volume.

Developing solvent solution: A mixture of 1-butanol, methanol, ethyl acetate, and ammonium hydroxide (11 : 3 : 3 : 3).

Procedure—Spot 10 µL each of the *Test solution* and the *Standard solution* onto the chromatographic plate, approximately 2 cm from the bottom and 2 cm apart. Allow the plate to air-dry. Place in a chromatographic chamber, and develop, allowing the developing solution to travel at least

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10 cm from the spotting line. Allow the plate to air-dry. View under shortwave light (254 nm). Didanosine appears as a blue spot.

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

Dissolution ⟨711⟩—[To come.]

Loss on drying ⟨731⟩—Dry 4 Tablets for 16 hours at 130°: they lose not more than 6% of their weight.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

0.01 M Ammonium acetate buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of 0.01 M ammonium acetate and methanol (99 : 1).

Standard stock solution—Transfer 25 mg of USP Didanosine Related Compound A RS to a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation.]

Standard solution—Transfer 3 mL of the *Standard stock solution* to a 250-mL volumetric flask. Dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation.]

Test solution—Proceed as directed for *Assay preparation.*

Diluted test solution—Dilute the *Test solution,* quantitatively and stepwise, if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution* as directed for *Procedure:* the retention time of didanosine related compound A is between 1.5 and 2.5 minutes; the column efficiency is not less than 1000 theoretical plates; and the relative standard deviation for replicate injection is not more than 5.0%. [NOTE—Didanosine related compound A is hypoxanthine.]

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Diluted test solution* into the chromatograph, record the chromatograms, and measure the responses of the major peaks, carrying out the chromatography for approximately 30 minutes. Calculate the percentage of didanosine related compound A in the portion of Tablets taken by the formula:

$$100(CVDL/N)(r_U / r_S)$$

in which C is the concentration of the USP Didanosine Related Compound A RS, in mg per mL, in the *Standard solution; V* is the volume, in mL, of the *Test solution; D* is the dilution factor of the *Diluted test solution; L* is the label claim of didanosine, in mg per Tablet; N is the number of the Tablets used to prepare the *Test solution;* and r_U and r_S are the peak responses obtained from the *Diluted test solution* and the *Standard solution,* respectively. Not more than 0.7% is found. Calculate the percentage of any other impurities by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of any other individual impurity obtained upon chromatographing the *Diluted test solution;* and r_s is the sum of the responses of all the peaks in the chromatogram of the *Diluted test solution,* including those of didanosine and hypoxanthine: not more than 0.2% of any other individual impurity is found; and not more than 1.2% of total impurities, excluding hypoxanthine, is found.

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Assay—

0.01 M Ammonium acetate buffer solution—Dissolve 1.54 g of ammonium acetate in a 2000-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of 0.01 M ammonium acetate and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution containing 0.1 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Assay preparation—Transfer not fewer than 5 crushed Tablets to a 500-mL volumetric flask. Dissolve in 250 mL of water, dilute with water to volume, and shake for about 10 minutes.

Diluted assay preparation—Dilute the *Assay preparation,* quantitatively and stepwise, if necessary, with water to obtain a solution containing about 0.1 mg per mL of didanosine. [NOTE—Use this solution within 72 hours of preparation; because of the buffering agents in the Tablets, the *Assay preparation* is stable longer than the *Standard preparation.*]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time of didanosine is greater than 3.0 minutes; 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 20 µL) of the *Standard preparation* and the *Diluted assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of didanosine ($C_{10}H_{12}N_4O_3$) by the formula:

$$[CVD(r_U / r_S)] / N$$

in which C is the concentration, in mg per mL, of USP Didanosine RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation; D* is the dilution factor of the *Diluted assay preparation;* r_U and r_S are the peak responses of the *Diluted assay preparation* and the *Standard preparation,* respectively; and N is the number of Tablets used to prepare the *Assay preparation.* ■2S (*USP29*)

BRIEFING

Digoxin Oral Solution, *USP 28* page 646. It is proposed to correct an error in the calculation in the *Assay.*

(DSB: G. Giancaspro) RTS—42834-1

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Digoxin Oral Solution

Former title: **Digoxin Elixir**

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and isopropyl alcohol (70 : 27.5 : 2.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Digoxin RS in diluted alcohol, and dilute quantitatively and stepwise with diluted alcohol to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Transfer an accurately measured volume

■of 10.0 mL■2S *(USP29)* of Elixir, equivalent to about 500 µg of digoxin, to a 25-mL volumetric flask, dilute with diluted alcohol to volume, and mix.

System suitability preparation—Prepare as directed in the *Assay* under *Digoxin*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-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 preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between digoxin and digoxigenin bisdigitoxoside is not less than 2.0; the tailing factor for the analyte peak 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 µg, of digoxin ($C_{41}H_{64}O_{14}$) in each mL of the Oral Solution taken by the formula:

~~$(100C/V)(r_U/r_S)$~~

■$2.5C(r_U / r_S)$■2S *(USP29)*

in which C is the concentration, in µg per mL, of USP Digoxin RS in the *Standard preparation;* ~~*V* is the volume, in mL, of Elixir taken;~~

■■2S *(USP29)* and r_U and r_S are the digoxin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

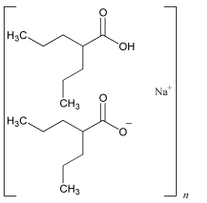
BRIEFING

Divalproex Sodium. Because there is no existing *USP* monograph for this drug substance, a new monograph is proposed. The proposed liquid chromatographic assay is based on analyses performed with the Agilent Eclipse XDB C8 brand of L7 column. Typical retention times are about 3 minutes for valproic acid related compound A and 5.2 minutes for valproic acid.

(PA3: R. Ravichandran; NL: L. Paul; PSD: C. Okeke) RTS—42281-1; 42281-2

Add the following:

■Divalproex Sodium



$(C_{16}H_{31}NaO_4)_n$ 310.41

Pentanoic acid, 2-propyl-, sodium salt (2 : 1).

Sodium hydrogen bis(2-propylvalerate), oligomer [*76584-70-8*].

» Divalproex Sodium contains not less than 98.0 percent and not more than 102.0 percent of $(C_{16}H_{31}NaO_4)_n$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers. Store at room temperature.

USP Reference standards ⟨11⟩—*USP Divalproex Sodium RS. USP Valproic Acid RS. USP Valproic Acid Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Ignite about 100 mg; the residue responds to the tests for *Sodium* ⟨191⟩.

Water, *Method I* ⟨921⟩**:** not more than 1.0%, determined on 3.0 g.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Residual solvents ⟨467⟩**:** meets the requirements.

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Assay—

Buffer—Dissolve 3.5 g of monobasic sodium phosphate monohydrate in 900 mL of water. Adjust with *o*-phosphoric acid to a pH of 3.5. Dilute with water to 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a 0.5% solution of sodium dodecyl sulfate in water.

Stock solution A—Transfer an accurately weighed amount of USP Valproic Acid RS to a suitable volumetric flask, first dissolve in methanol, using 10% of the final volume, then dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of about 5.0 mg per mL.

Stock solution B—Dissolve an accurately weighed amount of USP Valproic Acid Related Compound A RS in 2-propanol to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard preparation—Accurately transfer 20 mL of *Stock solution A* and 1 mL of *Stock solution B* into a 100-mL volumetric flask, and dilute with *Mobile phase* to obtain a solution having 1.0 mg per mL of valproic acid and 0.005 mg per mL of valproic acid related compound A.

Assay preparation—Transfer about 50 mg of Divalproex Sodium, accurately weighed, to a 100-mL volumetric flask; dissolve in 10 mL of methanol; and dilute with *Diluent* to volume. This solution has a concentration of about 0.5 mg per mL of divalproex sodium.

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 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 relative retention time for valproic acid related compound A is about 0.69, and that for valproic acid is 1.0; the resolution, *R,* between valproic acid related compound A and valproic acid is not less than 5.0; for the valproic acid peak, the column efficiency is not less than 5000 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 15 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 $(C_{16}H_{31}NaO_4)_n$ in the portion of Divalproex Sodium taken by the formula:

$$100(C_S / C_U)(r_U / r_S)(310.41/144.21)(1/2)$$

in which C_S is the concentration, in mg per mL, of valproic acid in the *Standard preparation;* C_U is the concentration of Divalproex Sodium, in mg per mL, in the *Assay preparation;* r_U and r_S are the peak areas for valproic acid obtained from the *Assay preparation* and the *Standard preparation;* 310.41 and 144.21 are the molecular weights for divalproex sodium and valproic acid, respectively; and 2 is the number of moles of valproic acid per mole of divalproex sodium.■2S (*USP29*)

BRIEFING

Ensulizole, *USP 28* page 735 and page 3221 of the *First Supplement.* It is proposed to replace the name of USP Ensulizole RS with USP Phenylbenzimidazole Sulfonic Acid RS to be consistent with the name used on the label for this Reference Standard.

(PA7b: B. Davani) RTS—42677-1

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Change to read:

USP Reference standards ⟨11⟩—~~*USP Ensulizole RS*~~

■*USP Phenylbenzimidazole Sulfonic Acid RS.*■2S *(USP29)*

BRIEFING

Estradiol and Norethindrone Acetate Tablets, page 1989 of *PF* 30(6) [Nov.–Dec. 2004]. On the basis of comments received, it is proposed to revise the *Chromatographic purity* test to increase each individual impurity limit in *Table 1* from 0.1% to 0.5% and in *Table 2* from 0.05% to 0.5%.

(PA1: C. Anthony; PSD: C. Okeke) RTS—43018-1

Add the following:

■Estradiol and Norethindrone Acetate Tablets

» Estradiol and Norethindrone Acetate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol ($C_{18}H_{24}O_2$) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of norethindrone acetate ($C_{22}H_{28}O_3$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Estradiol RS. USP Estrone RS. USP Norethindrone Acetate RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Place 2 Tablets into a 10-mL vial, and add 0.2 mL of water. When the Tablets are partially disintegrated, add a few glass beads, and shake vigorously to disintegration. Add 4.0 mL of dehydrated alcohol, and shake. Centrifuge until the supernatant is clear before application to the plate.

Standard solution—Dissolve accurately weighed quantities, of USP Estradiol RS and USP Norethindrone Acetate RS in dehydrated alcohol to obtain a solution having known concentrations of 0.5 mg per mL and 0.25 mg per mL, respectively.

Application volume: 2 µL.

Developing solvent solution: a mixture of chloroform and acetone (9 : 1).

Procedure—Proceed as directed in the chapter, using the *Developing solvent system*. After removal of the plate, mark the solvent front, and allow the solvent to evaporate. Place the plate on a heating plate at 100° for 15 minutes. Allow the plate to cool, and then immerse it in a mixture of dehydrated alcohol and concentrated sulfuric acid (95 : 5). Place the plate on a piece of thick horizontal paper until it is almost dry. Heat the plate at 100° until it has fully developed. Examine under UV light at 365 nm. The color and R_F value of the principal spots obtained from the *Test solution* correspond to those obtained from the *Standard solution*.

B: The retention time and UV spectrum 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.*

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Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g. The Tablets meet the requirements of the tests for the absence of *Salmonella species* and *Escherichia coli*.

Dissolution—[To come.]

Loss on drying ⟨731⟩—Dry about 1200 mg of finely powdered Tablets in a tared evaporating dish at a pressure not exceeding 25 mm of mercury at 60° for 3 hours: it loses not more than 7.5% of its weight.

Chromatographic purity—

Solution A—Prepare a mixture of water and tetrahydrofuran (200 : 1).

Solution B—Prepare a degassed solution of acetonitrile, water, and tetrahydrofuran (160 : 40 : 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—Prepare a mixture of water and dehydrated alcohol (1 : 1).

System suitability solution—Dissolve accurately weighed quantities of USP Estradiol RS, USP Norethindrone Acetate RS, and USP Estrone RS in *Diluent* to obtain a solution having known concentrations of about 240 µg per mL, 60 µg per mL, and 1 µg per mL, respectively.

Test solution—Accurately weigh and finely powder 20 Tablets. Transfer the equivalent of 12 Tablets to an appropriate flask, and dissolve in a known volume of *Diluent* to obtain a solution having known concentrations of estradiol and norethindrone acetate of about 240 µg per mL and 120 µg per mL, respectively. Filter the solution, if necessary.

Estradiol standard stock solution—Dissolve an accurately weighed quantity of USP Estradiol RS in alcohol to obtain a solution having a known concentration of estradiol of about 250 µg per mL.

Norethindrone acetate standard stock solution—Dissolve an accurately weighed quantity of USP Norethindrone Acetate RS in alcohol to obtain a solution having a known concentration of norethindrone acetate of about 150 µg per mL.

Standard solution—Combine 250 µL of *Estradiol standard stock solution* and 100 µL of *Norethindrone acetate standard stock solution,* and dilute with 50.0 mL of *Diluent*.

Chromatographic system—The liquid chromatograph is equipped with a dual wavelength detector (235 nm and 254 nm) and a 3.9- × 30-cm column that contains 4-µm packing L1. The flow rate is about 0.8 mL per minute. Program the chromatogram as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	80	20	equilibration
0–2	80→65	20→35	linear gradient
2–35	65→20	35→80	linear gradient
35–49	20	80	isocratic
49–50	20→80	80→20	linear gradient
50–60	80	20	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.4 for estrone, about 3.0 for norethindrone acetate, and 1.0 for estradiol. The resolution, *R,* between estrone and estradiol is not less than 1.3, measured at 254 nm.

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

peak responses. Calculate the percentage of any estradiol impurity in the portion of Tablets taken by the formula:

$$100F(C_S / C_T)(r_i / r_S)$$

in which F is the relative response factor of any estradiol impurity relative to estradiol; C_S and C_T are the concentrations of the *Standard solution* and the *Test solution,* respectively; r_i is the peak area at 235 nm for each impurity obtained from the *Test solution;* and r_S is the peak area at 235 nm obtained from the *Standard solution*. The Tablets meet the requirements given in *Table 1*. Not ~~more than 0.1% of any other impurity is found, and~~ more than 1.0% of total impurities is found. Calculate the percentage of any norethindrone acetate related impurities in the portion of Tablets taken by the formula:

$$100F(C_S / C_T)\ (r_i / r_S)$$

in which F is the relative response factor of any norethindrone acetate related impurity relative to norethindrone acetate; C_S and C_T are the concentrations of the *Standard solution* and the *Test solution,* respectively; r_i is the peak area at 254 nm for each impurity obtained from the *Test solution;* and r_S is the peak area at 254 nm obtained from the *Standard solution*. The Tablets meet the requirements given in *Table 2*. Not ~~more than 0.5% of any other impurity is found, and not~~ more than 1.0% of total impurities is found.

Table 1

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
6-α Hydroxyl estradiol	about 0.47	1.0	~~0.1~~ 0.5
6-β Hydroxyl estradiol	about 0.51	1.0	~~0.1~~ 0.5
6-Keto estradiol	about 0.62	1.0	~~0.1~~ 0.5
16-Keto estradiol	about 0.65	1.0	~~0.1~~ 0.5
6-Keto estrone	about 0.75	1.0	~~0.1~~ 0.5
β-Equilenol	about 0.88	0.04	~~0.1~~ 0.5
6-Dehydro estradiol	about 0.95	1.0	~~0.1~~ 0.5
Estradiol	1.0	1.0	~~0.1~~ 0.5
α-Estradiol	about 1.06	1.0	~~0.1~~ 0.5
Estrone	about 1.17	1.0	~~0.1~~ 0.5
4-Methyl estradiol	about 1.24	1.0	~~0.1~~ 0.5

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Table 2

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
6-β Hydroxy-norethindrone acetate	about 0.58	1.0	~~0.05~~ 0.5
Norethindrone	about 0.66	1.0	~~0.05~~ 0.5
6-Keto-norethindrone acetate	about 0.79	1.8	~~0.05~~ 0.5
19-Nor-17-alpha-preg-4-ene-3,20-dione	about 0.90	1.0	~~0.05~~ 0.5
6-Dehydro-norethindrone acetate	about 0.97	2.2	~~0.05~~ 0.5
Norethindrone acetate	about 1.0	1.0	~~0.05~~ 0.5

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (55 : 45) (see *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of water and dehydrated alcohol (1 : 1).

Estrone standard stock solution—Transfer about 6.00 mg of USP Estrone RS, accurately weighed, to a 50-mL volumetric flask, and dissolve in 10 mL of dehydrated alcohol. Dilute with dehydrated alcohol to volume, and mix.

Estradiol standard stock solution—Prepare a solution of USP Estradiol RS in dehydrated alcohol having a known concentration of 0.25 mg per mL.

Norethindrone acetate standard stock solution—Prepare a solution of USP Norethindrone Acetate RS in dehydrated alcohol having a known concentration of 0.15 mg per mL.

System suitability preparation—Transfer 800 µL of *Estradiol standard stock solution,* 600 µL of *Norethindrone acetate standard stock solution,* and 200 µL of *Estrone standard stock solution* to a suitable flask containing 10.0 mL of *Diluent*.

Standard preparation—Prepare a solution of *Estradiol standard stock solution* and *Norethindrone acetate standard stock solution* in *Diluent* having an accurately known concentration of about 20 µL per ml and 10 µL per mL, respectively.

Assay preparation—Add 12 Tablets into a measured amount of *Diluent,* to obtain a solution having an estradiol concentration of about 20 µL per mL and a norethindrone acetate concentration of about 10 µL per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode array detector and a 4.6- × 150-mm column that contains packing L1. The flow rate is about 1.0 mL per minute. Perform an investigational run to determine the retention times for estradiol and norethindrone acetate. Thus, the absorption of estradiol at 280 nm and norethindrone acetate at 254 nm can be included in a single run by altering the wavelength. Chromatograph the *System suitability preparation,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between estradiol and estrone acetate is not less than 1.8. Chromatograph the *Standard preparation,* and record the peak area as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3%.

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 estradiol and norethindrone acetate peaks. Calculate the quantity, in mg, of estradiol ($C_{18}H_{24}O_2$) in each of the Tablets taken by the formula:

$$(VC/12)(r_U/r_S)$$

in which V is the volume, in mL, of *Diluent* taken to prepare the *Assay preparation; C* is the concentration, in mg per mL, of USP Estradiol 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. Calculate the quantity, in mg, of norethindrone acetate ($C_{22}H_{28}O_3$) in each of the Tablets taken by the formula:

$$(VC/12)(r_U/r_S)$$

in which V is the volume, in mL, of *Diluent* used in the *Assay preparation; C* is the concentration, in mg per mL, of USP Norethindrone Acetate 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 (*USP29*)

BRIEFING

Ethyl Chloride, *USP 28* page 796. It is proposed to delete the test for *Alcohol* because it includes an odor test that has potential safety concerns.

(PA1: K. Russo) RTS—42915-2

Delete the following:

■~~**Alcohol**—To the liquid obtained in the test for *Reaction* add a few drops of potassium dichromate TS and 2 mL of 2 N sulfuric acid, and boil the mixture: no odor of acetaldehyde is perceptible, and no greenish or purplish color is produced.~~■2S (*USP29*)

BRIEFING

Fluconazole, *USP 28* page 828 and page 408 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to delete the test for *Melting range* because this test is not specific to compounds exhibiting polymorphism. Additionally, there are already adequate tests for *Identification* (IR and UV) in this monograph.

(PA7b: B. Davani) RTS—42279-1

Change to read:

» Fluconazole contains not less than ~~98.5~~

▲98.0▲*USP29*
percent and not more than ~~101.5~~

▲102.0▲*USP29*
percent of $C_{13}H_{12}F_2N_6O$, calculated on the dried basis.

Add the following:

▲**Labeling**—If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test(s) the article complies.▲*USP29*

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Desacetyl Diltiazem Hydrochloride RS.*▲*USP29*
USP Fluconazole RS. USP Fluconazole Related Compound A RS. USP Fluconazole Related Compound B RS. USP Fluconazole Related Compound C RS.

Delete the following:

■~~**Melting range** ⟨741⟩: between 138° and 142°.~~■2S (*USP29*)

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Change to read:

Related compounds—

▲[NOTE—On the basis of information regarding the manufacturing process, perform either *Test 1* or *Test 2* and *Test 3*.]

TEST 1—▲*USP29*

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

System suitability solution—Use the *Standard solution*.

Standard solution—Transfer accurately weighed quantities of USP Fluconazole RS, USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, and USP Fluconazole Related Compound C RS to a suitable volumetric flask, dissolve in acetonitrile, dilute quantitatively, and stepwise if necessary, with *Mobile phase* to volume, and mix to obtain a solution having known concentrations of 10 µg of each per mL.

Test solution—Transfer about 30 mg of Fluconazole, 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 260-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L1. The flow rate is about 0.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* typical retention times are about 4.9 minutes for fluconazole related compound A, 8.0 minutes for fluconazole related compound B, 8.5 minutes for fluconazole related compound C, and 9.9 minutes for fluconazole; the resolution, *R,* between fluconazole related compound B and fluconazole related compound C is not less than 1.5; and the relative standard deviation of each peak 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, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fluconazole related compound A, fluconazole related compound B, fluconazole related compound C, and any other impurities in the portion of Fluconazole taken by the formula:

$$1000(C/W)(r_U/r_S)$$

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

▲not more than 1.0% of any impurity with a relative retention time (RRT) of about 0.6 is found; not more than 0.2% of any impurity with an RRT of 0.5 or an RRT of about 0.9 is found; not more than 0.1% of any other individual impurity is found; not more than 0.2% of total other impurities is found; and not more than 1.2% of total impurities is found.

TEST 2—

Acetate buffer—Prepare a 0.04 M anhydrous sodium acetate solution, adjust with 1 N acetic acid to a pH of 5.0, and mix.

Solution A: filtered and degassed *Acetate buffer*.

Solution B: acetonitrile.

Solution C: methanol.

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

Diluent—Prepare a mixture of *Acetate buffer* and methanol (84 : 16).

Standard solution—Dissolve an accurately weighed quantity of USP Fluconazole RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.01 mg per mL.

System suitability solution—Dissolve suitable quantities of USP Fluconazole RS and USP Desacetyl Diltiazem Hydrochloride RS in *Diluent.* Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution containing about 0.02 mg per mL and 0.006 mg per mL, respectively.

Test solution—Transfer about 200 mg of Fluconazole, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 261-nm detector and a 4.0-mm × 10-cm column that contains packing L1. The flow rate is 1 mL per minute. The chromatograph is programmed as follows.

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Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–10	80	5	15	isocratic
10–20	80→30	5→55	15	linear gradient (*A* and *B*)
20–23	30	55	15	isocratic
23–25	30→80	55→5	15	reset composition
25–30	80	5	15	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the relative retention times are 1.0 for fluconazole and about 1.2 for desacetyl hydrochloride; the resolution, *R,* between fluconazole and desacetyl diltiazem hydrochloride is not less than 10.0; the column efficiency for fluconazole is not less than 30,000 theoretical plates; and the tailing factor, *T,* is not more than 1.4. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is less 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, and measure the peak responses. Calculate the percentage of each impurity in the portion of Fluconazole taken by the formula:

$$10{,}000(r_i / r_S)(C/W)(1/F)$$

in which r_i is the peak response of each impurity obtained from the *Test solution;* r_S is the peak response of fluconazole obtained from the *Standard solution; C* is the concentration, in mg per mL, of USP Fluconazole RS in the *Standard solution; W* is the weight, in mg, of Fluconazole taken to prepare the *Test solution;* and *F* is the relative response factor as determined from the following table.

Relative Response Factor (*F*)	Relative Retention Time (RRT)
0.72	0.17–0.37
0.85	1.20–1.32
1.21	0.48–0.60
0.96	1.14–1.18
0.97	0.67–0.79
1.0	all other peaks

Not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

TEST 3—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve an accurately weighed quantity of Fluconazole in methanol to obtain a solution containing approximately 50 mg per mL.

Standard solutions—Dissolve an accurately weighed quantity of USP Fluconazole RS in methanol to obtain *Standard solution A* having a known concentration of about 1 mg per mL (2.0%). Quantitatively dilute portions of this solution with methanol to obtain *Standard solution B* and *Standard solution C* having known concentrations of about 0.1 mg per mL (0.2%) and 0.05 mg per mL (0.1%), respectively.

Developing solvent system—Prepare a mixture of chloroform, methanol, and ammonium hydroxide (80 : 20 : 1).

Application volume: 10 µL.

Spray reagent A—Dissolve about 170 mg of silver nitrate in 100 mL of water.

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Spray reagent B (Potassium iodoplatinate solution)—Dissolve about 375 mg of chloroplatinic acid in 5 mL of 1 N hydrochloric acid. Dissolve about 5 g of potassium iodide in 50 mL of water, and store in a light-resistant container. Prepare a mixture of water, the potassium iodide solution, and the chloroplatinic acid solution (20 : 9 : 1).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Spray the dry plate with *Spray reagent A,* and expose the plate to 365-nm UV light for 10 to 20 minutes. Dry the plate for 20 minutes between 80° and 90°, then spray the plate with *Spray reagent B*. Allow the plate to dry. Examine the plate 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:* no spot from the chromatogram of the *Test solution* with an R_F value of between 0.10 to 0.25 and 0.27 to 0.41 is larger or more intense than that obtained from *Standard solution B* (0.2%).▲*USP29*

BRIEFING

Fluorometholone Acetate. 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 the Merck Hibar 11 C18 brand of L1 column.

(PA1: C. Anthony) RTS—13634-1

Add the following:

■Fluorometholone Acetate

$C_{24}H_{31}FO_5$ 418.50

» Fluorometholone Acetate contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{31}FO_5$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—***USP Fluorometholone RS. USP Fluorometholone Acetate RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩.

Solution: 10 µg per mL.

Medium: methanol.

Absorptivities, calculated on the dried basis, do not differ by more than 3.0%.

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩.

Adsorbent: 0.20-mm layer of chromatographic silica gel mixture containing a fluorescent indicator.

Application volume: 2 µL.

Developing solvent system: chloroform and methanol (19 : 1).

Specific rotation ⟨781S⟩**:** between +25.0° and +31.0°.

Test solution: 20 mg per mL, in chloroform.

Loss on drying ⟨731⟩—Dry in vacuum at 60° for 3 hours: it loses not more than 1.0% of its weight.

Chromatographic purity—

Mobile phase, Standard preparation, Resolution solution, Assay preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

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Procedure—Proceed as directed for *Procedure* in the *Assay.* [NOTE—Allow the elution to continue for about four times the elution time of the fluorometholone acetate peak before making the next injection.] Calculate the percentage of each impurity in the portion of Fluorometholone Acetate taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak area for each impurity, and r_s is the sum of the peak areas of all the peaks: not more than 1.0% of fluorometholone and not more than 0.5% of any other individual impurity is found, and not more than 2.0% total impurities is found.

Residual solvents ⟨467⟩**:** meets the requirements.

Solvent: dimethyl sulfoxide.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Fluorometholone Acetate 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.

Resolution solution—Prepare a solution of USP Fluorometholone RS in acetonitrile having a concentration of about 1 mg per mL. Mix equal volumes of this solution and the *Standard preparation.*

Assay preparation—Transfer about 50 mg of Fluorometholone Acetate, accurately weighed, to a 50-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 254-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 relative retention time is about 0.6 for fluorometholone and 1.0 for fluorometholone acetate; the resolution, *R,* between fluorometholone and fluorometholone acetate is not less than 4.0. Chromatograph the *Standard preparation* and record the peak responses as directed for *Procedure:* the tailing factor for fluorometholone acetate is not more than 2.0; the relative standard deviation for replicate injections is not more than 2.0% in the *Standard preparation.*

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 $C_{24}H_{31}FO_5$, in the portion of Fluorometholone Acetate taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluorometholone Acetate 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 (*USP29*)

BRIEFING

Hyoscyamine Sulfate Elixir, *USP 28* page 987 and page 3245 of the *First Supplement;* **Hyoscyamine Sulfate Injection,** *USP 28* page 987 and page 3245 of the *First Supplement;* **Hyoscyamine Sulfate Oral Solution,** *USP 28* page 988 and page 3246 of the *First Supplement;* **Hyoscyamine Sulfate Tablets,** *USP 28* page 988 and page 3246 of the *First Supplement.* It is proposed to revise the *Identification* tests by replacing the wet chemistry tests with

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HPLC retention time agreement of the major peak in the *Assay preparation* and the *Standard preparation*. The proposed revision is consistent with current pharmaceutical industry practice.

(PA4: E. Gonikberg) RTS—42756-1

Change to read:

Identification—

~~**A:** Transfer a quantity of Elixir, equivalent to about 1.25 mg of hyoscyamine sulfate, to a separator. Render alkaline with 6 N ammonium hydroxide, and extract with 50 mL of methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Add 2 drops of nitric acid to the dry residue, and evaporate on a steam bath to dryness. Add a few drops of alcoholic potassium hydroxide TS: a violet color appears.~~

~~**B:** Transfer a quantity of Elixir, equivalent to about 2.5 mg of hyoscyamine sulfate, to a separator. Render acidic with 3 N sulfuric acid, and extract with methylene chloride. Discard this extract. Render the solution alkaline with 6 N ammonium hydroxide, and extract with methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Dissolve the residue in a small amount of 0.1 N hydrochloric acid, and add gold chloride TS, with shaking, until a definite precipitate separates. Slowly heat until the precipitate dissolves, and allow the solution to cool: lustrous golden yellow scales are formed.~~

■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 (*USP29*)

BRIEFING

Hyoscyamine Sulfate Injection, *USP 28* page 987 and page 3245 of the *First Supplement*—See briefing under *Hyoscyamine Sulfate Elixir.*

(PA4: E. Gonikberg) RTS—42756-2

Change to read:

Identification—

~~**A:** Transfer a volume of Injection, equivalent to about 2.5 mg of hyoscyamine sulfate, to a separator. Render alkaline with 6 N ammonium hydroxide, and extract with 25 mL of methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Add 2 drops of nitric acid to the dry residue, and evaporate on a steam bath to dryness. Add a few drops of alcoholic potassium hydroxide TS: a violet color is produced.~~

~~**B:** Transfer a volume of Injection, equivalent to about 2.5 mg of hyoscyamine sulfate, to a separator. Render the solution acidic with 3 N sulfuric acid, and extract with 30 mL of methylene chloride. Discard the extract. Render the solution alkaline with 6 N ammonium hydroxide, and extract with 30 mL of methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Dissolve the residue in a small amount of 0.1 N hydrochloric acid, and add gold chloride TS, with shaking, until a definite precipitate separates. Heat until the precipitate dissolves, and allow the solution to cool: lustrous golden yellow scales are formed.~~

■**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.*■2S (*USP29*)

~~**C:**~~

■**B:**■2S (*USP29*)
After evaporation to dryness, or appropriate adjustment of concentration, it responds to the tests for *Sulfate* ⟨191⟩.

~~**D:**~~

■**C:**■2S (*USP29*)
The angular rotation of the Injection is levorotatory.

BRIEFING

Hyoscyamine Sulfate Oral Solution, *USP 28* page 987 and page 3246 of the *First Supplement*—See briefing under *Hyoscyamine Sulfate Elixir.*

(PA4: E. Gonikberg) RTS—42756-3

Change to read:

Identification—

~~**A:** Transfer a quantity of Oral Solution, equivalent to about 1.25 mg of hyoscyamine sulfate, to a separator. Render alkaline with 6 N ammonium hydroxide, and extract with 10 mL of methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Add 2 drops of nitric acid to the dry residue, and evaporate on a steam bath to dryness. Add a few drops of alcoholic potassium hydroxide TS: a violet color is produced.~~

~~**B:** Transfer a quantity of Oral Solution, equivalent to about 2.5 mg of hyoscyamine sulfate, to a separator. Render the solution acidic with 3 N sulfuric acid, and extract with methylene chloride. Discard the extract. Render the solution alkaline with 6 N ammonium hydroxide, and extract with methylene chloride, filtering the extract into a beaker. Evaporate to dryness. Dissolve the residue in a small amount of 0.1 N hydrochloric acid, and add gold chloride TS, with shaking, until a definite precipitate separates. Slowly heat until the precipitate dissolves, and allow the solution to cool: lustrous golden yellow scales are formed.~~

■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 (*USP29*)

BRIEFING

Hyoscyamine Sulfate Tablets, *USP 28* page 988 and page 3246 of the *First Supplement*—See briefing under *Hyoscyamine Sulfate Elixir.*

(PA4: E. Gonikberg) RTS—42756-4

Change to read:

Identification—~~Macerate a quantity of powdered Tablets, equivalent to about 5 mg of hyoscyamine sulfate, with 20 mL of water, and transfer to a separator. Make the solution alkaline with 6 N ammonium hydroxide, and extract the alkaloid with 50 mL of chloroform. Filter the chloroform layer, divide it into two equal portions, and evaporate each to dryness. Perform tests *A* and *B* on the residues.~~

~~**A:** To one portion of the dry residue add 2 drops of nitric acid, evaporate on a steam bath to dryness, and add a few drops of alcoholic potassium hydroxide TS: a violet color is produced.~~

~~**B:** Dissolve the other portion of the residue in 1 mL of 0.1 N hydrochloric acid, and add gold chloride TS, dropwise with shaking, until a definite precipitate separates. Slowly heat until the precipitate dissolves, and allow the solution to cool: lustrous golden yellow scales are formed.~~

■**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.*■2S (*USP29*)

~~**C:**~~

■**B:**■2S (*USP29*)
A filtered solution of Tablets responds to the tests for *Sulfate* ⟨191⟩.

BRIEFING

Ibuprofen Tablets, *USP 28* page 993. To obtain the specified concentration of 4-isobutylacetophenone, it is proposed to revise the *Assay* to adjust the volume of the *Internal standard solution* used to prepare the *4-Isobutylacetophenone standard solution*.

(PA2: C. Anthony) RTS—42727-1

Change to read:

Assay—

Mobile phase, Internal standard solution, and *Standard preparation*—Prepare as directed in the *Assay* under *Ibuprofen*.

4-Isobutylacetophenone standard solution—Quantitatively dissolve an accurately weighed quantity of 4-isobutylacetophenone in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to ~~100 mL of *Internal standard solution,*~~

■a 100-mL volumetric flask, dilute with *Internal standard solution* to volume,■2S (*USP29*)
and mix to obtain a solution having a known concentration of about 0.012 mg ~~of 4-isobutylacetophenone~~

■■2S (*USP29*)
per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1200 mg of ibuprofen, to a suitable container, add 100.0 mL of *Internal standard solution,* and shake for 10 minutes. [NOTE—Where the Tablets are coated, place an accurately counted number of Tablets, equivalent to not less than 1200 mg of ibuprofen, in a container, add an accurately measured volume of *Internal standard solution*, sufficient to obtain an *Assay preparation* containing about 12 mg of ibuprofen per mL, and about 15 glass beads, and shake until the Tablets are completely disintegrated.] Centrifuge a portion of the suspension so obtained, and use the clear supernatant as the *Assay preparation*.

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 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for ibuprofen and 1.0 for valerophenone; the tailing factors for the individual peaks are not more than 2.5; the resolution, *R,* between the ibuprofen peak and the valerophenone peak is not less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *4-Isobutylacetophenone standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for 4-isobutylacetophenone; the tailing factors for the individual peaks are not more than 2.5; the resolution, *R,* between valerophenone and 4-isobutylacetophenone is not less than 2.5; 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 preparation,* the *Assay preparation,* and the *4-Isobutylacetophenone standard solution* into the chromatograph, record the

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chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ibuprofen ($C_{13}H_{18}O_2$) in each Tablet taken by the formula:

$$100C(A/W)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation; A* is the average weight, in mg, of a Tablet; W is the weight, in mg, of Tablet powder taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the ibuprofen peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation,* respectively. Where intact Tablets were taken, calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in each Tablet by the formula:

$$(CV/N)(R_U/R_S)$$

in which V is the volume, in mL, of *Internal standard solution* used to prepare the *Assay preparation; N* is the number of Tablets taken; and the other terms are as defined above.

BRIEFING

Insulin, *USP 28* page 1020; **Insulin Human,** *USP 28* page 1022. Because of difficulties in obtaining proinsulin reference materials and the lack of specific tests, it is proposed that references to *USP Proinsulin (Beef) RS* and *USP Proinsulin (Pork) RS* be deleted from the monograph.

(BNT: L. Callahan) RTS—43019-1

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Insulin RS. USP Insulin (Beef) RS. USP Insulin (Pork) RS.* ~~*USP Proinsulin (Beef) RS. USP Proinsulin (Pork) RS.*~~

■■2S (*USP29*)

BRIEFING

Insulin Human, *USP 28* page 1022—See briefing under *Insulin*. The USP Insulin (Pork) RS is also deleted from the monograph because there is no specific reference to this material in the monograph.

(BNT: L. Callahan) RTS—43019-02

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Insulin Human RS.* ~~*USP Insulin (Pork) RS. USP Proinsulin (Pork) RS.*~~

■■2S (*USP29*)

BRIEFING

Isopropyl Alcohol, *USP 28* page 1077. Because USP Isopropyl Alcohol RS has recently become available, it is proposed to add a *USP Reference standards* ⟨11⟩ section and to replace the current *Identification* test with *Infrared Absorption* ⟨197F⟩, using the USP Reference Standard.

(PA7b: B. Davani) RTS—42678-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Isopropyl Alcohol RS.*■2S (*USP29*)

Change to read:

Identification— ~~The IR absorption spectrum of a thin film of it exhibits a strong broad band at 3.0 µm; a strong region of absorption between 3.35 and 3.5 µm, with its highest peak at about 3.36 µm, and others at about 3.41 and 3.47 µm; a strong region of absorption between 6.7 and 7.8 µm, the most prominent features being the peaks at about 6.80, 7.10, 7.25 (the highest), 7.50, and 7.65 µm; a strong region of absorption between 8.5 and 9.2 µm, peaking at about 8.6, 8.85, and 9.0 µm; and strong peaks at about 10.5 and 12.3 µm.~~

■*Infrared Absorption* ⟨197F⟩.■2S (*USP29*)

BRIEFING

Isosorbide Dinitrate Tablets, *USP 28* page 1087; **Isosorbide Dinitrate Chewable Tablets,** *USP 28* page 1087; **Isosorbide Dinitrate Extended-Release Tablets,** *USP 28* page 1087 and page 3494 of the *Second Supplement;* **Isosorbide Dinitrate Sublingual Tablets,** *USP 28* page 1088 and page 113 of *PF* 30(1) [Jan.–Feb. 2004]. It is proposed to correct the name of the USP Reference Standard used in the test for *Dissolution* and the *Assay.*

(PA5: A. Wilk) RTS—42894-1

Change to read:

Dissolution ⟨711⟩—

Medium: water; 1000 mL.
Apparatus 2: 75 rpm.
Time: 45 minutes.

Mobile phase—Prepare a suitable degassed and filtered mixture of pH 3.0, 0.1 M ammonium sulfate and methanol (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩), using sulfuric acid for any necessary pH adjustment.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 1.0 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%, and the tailing factor is not more than 1.5.

Procedure—Separately inject equal volumes (about 20 µL) of the Standard solution and a filtered aliquot of the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution having a known concentration of USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS, similarly prepared and chromatographed.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_6H_8N_2O_8$ is dissolved in 45 minutes.

Change to read:

Assay—

Buffer solution, Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Diluted Isosorbide Dinitrate*.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg of isosorbide dinitrate, to a dry, 50-mL volumetric flask, add about 30 mL of *Mobile phase,* and shake the mixture by hand immediately, to prevent clumping. If clumping persists, disperse with the aid of sonication, or break the aggregates with a stirring rod. Shake for 30 minutes. Add 8.0 mL of *Internal standard solution,* cool to room temperature, add 8 mL of a 1 in 10 dilution of *Buffer solution* in water, dilute with *Mobile phase* to volume, and mix. Pass a portion through a disposable ion-exchange filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Isosorbide Dinitrate*. Calculate the quantity, in mg, of $C_6H_8N_2O_8$ 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 isosorbide dinitrate from the USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS taken for the *Standard preparation;* and R_U and R_S are the ratios of the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Isosorbide Dinitrate Chewable Tablets, *USP 28* page 1087—See briefing under *Isosorbide Dinitrate Tablets*.

(PA5: A. Wilk) RTS—42894-2

Change to read:

Assay—

Buffer solution, Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Diluted Isosorbide Dinitrate*.

Assay preparation—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg of isosorbide dinitrate, to a dry, 50-mL volumetric flask, add about 30 mL of *Mobile phase,* and shake the mixture by hand immediately, to prevent clumping. If clumping persists, disperse with the aid of sonication, or break the aggregates with a stirring rod, or warm on a steam bath while keeping the flask stoppered, or allow the flask to stand until the clumps dissipate. [NOTE—If clumping still continues, discard the mixture, and instead disperse an accurately weighed test portion in 15 mL of a 1 in 10 dilution of *Buffer solution* in water by heating on a steam bath for 1 hour with frequent shaking, then add 15 mL of methanol.] Shake for 30 minutes. Add 8.0 mL of *Internal standard solution,* cool to room temperature, add 8 mL of a 1 in 10 dilution of *Buffer solution* in water, dilute with *Mobile phase* to volume, and mix. Pass a portion through a microporous membrane filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Isosorbide Dinitrate*. Calculate the quantity, in mg, of $C_6H_8N_2O_8$ in the portion of Chewable Tablets taken by the formula:

$$50C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of isosorbide dinitrate from the USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS taken for the *Standard preparation;* and R_U and R_S are the ratios of the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Isosorbide Dinitrate Extended-Release Tablets, *USP 28* page 1087 and page 3494 of the *Second Supplement*—See briefing under *Isosorbide Dinitrate Tablets.*

(PA5: A. Wilk) RTS—42894-3

Change to read:

Assay—

Buffer solution, Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Diluted Isosorbide Dinitrate*.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg of isosorbide dinitrate, to a dry, 50-mL volumetric flask, add about 30 mL of *Mobile phase,* and shake the mixture by hand immediately, to prevent clumping. If clumping persists, disperse with the aid of sonication, or break the aggregates with a stirring rod, or warm on a steam bath while keeping the flask stoppered, or allow the flask to stand until the clumps dissipate. [NOTE—If clumping still continues, discard the mixture, and instead disperse an accurately weighed test portion in 15 mL of a 1 in 10 dilution of *Buffer solution* in water by heating on a steam bath for 1 hour with frequent shaking, then add 15 mL of methanol.] Shake for 30 minutes. Add 8.0 mL of *Internal standard solution,* cool to room temperature, add 8 mL of a 1 in 10 dilution of *Buffer solution* in water, dilute with *Mobile* to volume, and mix. Pass a portion through a microporous membrane filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Isosorbide Dinitrate*. Calculate the quantity, in mg, of $C_6H_8N_2O_8$ 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 isosorbide dinitrate from the USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS taken for the *Standard preparation;* and R_U and R_S are the ratios of the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Isosorbide Dinitrate Sublingual Tablets, *USP 28* page 1088 and page 113 of *PF* 30(1) [Jan.–Feb. 2004]—See briefing under *Isosorbide Dinitrate Tablets*.

(PA5: A. Wilk) RTS—42894-4

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

■■2S (*USP29*)
⟨711⟩—
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Time: 20 minutes.

Mobile phase—Prepare a suitable degassed and filtered mixture of pH 3.0, 0.1 M ammonium sulfate and methanol (50 : 50).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, prepared as directed below, 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—

■Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled samples as the test solution.■2S (*USP29*)
Separately inject equal volumes (about 20 µL) of the Standard solution and an ~~filtered~~

■■2S (*USP29*)
aliquot of the ~~solution under test~~

■pooled sample■2S (*USP29*)
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_6H_8N_2O_8$ dissolved in comparison with a Standard solution having a known concentration of USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS, similarly prepared and chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_6H_8N_2O_8$ is dissolved in 20 minutes:

■the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1, or S_2. The quantity, *Q,* is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

■2S (*USP29*)

In-Process Revision

Change to read:

Assay—

Buffer solution, Mobile phase, Internal standard solution, Standard preparation, and *Chromatographic system*—Prepare as directed in the *Assay* under *Diluted Isosorbide Dinitrate*.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg of isosorbide dinitrate, to a 50-mL volumetric flask, add about 30 mL of *Mobile phase,* and shake for 30 minutes. Add 8.0 mL of *Internal standard solution,* cool to room temperature, add 8 mL of a 1 in 10 dilution of *Buffer solution* in water, dilute with *Mobile phase* to volume, and mix. Filter a portion through a 0.45-µm filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Isosorbide Dinitrate*. Calculate the quantity, in mg, of $C_6H_8N_2O_8$ 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 isosorbide dinitrate from the USP

■Diluted■2S (*USP29*)
Isosorbide Dinitrate RS taken for the *Standard preparation;* and R_U and R_S are the ratios of the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ketoprofen Extended-Release Capsules. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the Prodigy ODS(3) brand of L1 column. Typical retention times are about 11.4 minutes for ketoprofen and about 17.2 minutes for ketoprofen related compound A.

(PA2: C. Anthony) RTS—39383-1

In-Process Revision

Add the following:

■Ketoprofen Extended-Release Capsules

» Ketoprofen Extended-Release Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ketoprofen ($C_{16}H_{14}O_3$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Ketoprofen RS. USP Ketoprofen Related Compound A 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: The UV spectrum obtained from the *Sample preparation* of the drug release procedure corresponds to the spectrum obtained from the *Standard preparation.*

Water, *Method I* ⟨921⟩**:** not more than 3.0%.

Drug release, *Method B* ⟨724⟩**—**[To come].

Uniformity of dosage units ⟨905⟩**:** meets the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—[NOTE—The *Standard solution* and *Test solution* must be protected from light.]

Mobile phase and *Resolution*—Proceed as directed in the *Assay.*

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

Test solution—Transfer the contents of 10 Capsules, 1 Capsule each, to each of ten 250-mL volumetric flasks, add about 150 mL of *Mobile phase* to each flask, and stir for 2 hours. Dilute with *Mobile phase* to volume, and mix. Centrifuge, and pipet a volume of clear supernatant that contains about 2.4 mg of ketoprofen into a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *Reso-*

lution solution, and record the responses as directed for *Procedure*: the resolution, *R,* between ketoprofen and ketoprofen related compound A is not less than 3.0; and the tailing factor for the ketoprofen peak is not more than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six 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 major peak responses. Calculate the percent of $C_{16}H_{14}O_3$ in each Capsule by the formula:

$$(TC/D)(r_U / r_S)$$

in which T is the labeled quantity, in mg, of ketoprofen in the Capsule; C is the concentration, in mg per mL, of ketoprofen in the *Standard solution; D* is the concentration, in mg per mL, of ketoprofen in the *Test solution* based upon the labeled quantity per Capsule and the extent of dilution; and r_U and r_S are the ketoprofen peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Assay—[NOTE—The *Standard preparation* and *Assay preparation* must be protected from light.]

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (110 : 90 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution containing about 0.25 mg per mL of USP Ketoprofen RS and 0.5 mg per mL of USP Ketoprofen Related Compound A RS in *Mobile phase.* Pipet 4.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Transfer about 24 mg of USP Ketoprofen RS, accurately weighed, to a 100-mL volumetric flask, add 25 mL of *Mobile phase,* and mix. 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.

Assay preparation—Remove completely the contents of not fewer than 20 Capsules, and accurately transfer a quantity of the beads equal to about 200 mg of ketoprofen to a 250-mL volumetric flask. Add 150 mL of *Mobile phase* to volume, and mix. Centrifuge, and pipet 3.0 mL of clear supernatant that contains about 2.4 mg of ketoprofen into a 200-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 5-µm L1 packing. The flow rate is about 1.2 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ketoprofen and ketoprofen related compound A is not less than 3.0; and the tailing factor for the ketoprofen peak 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 of the *Standard preparation* 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 ketoprofen ($C_{16}H_{14}O_3$) in the portion of Capsules taken by the formula:

$$CD(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Ketoprofen RS in the *Standard preparation; D* is the dilution

factor used in preparing the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

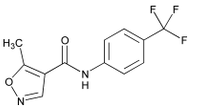
BRIEFING

Leflunomide. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Symmetry brand of L1 column.The typical retention time is about 28 minutes for leflunomide.

(PA2: C. Anthony) RTS—41078-1

Add the following:

■Leflunomide



$C_{12}H_9F_3N_2O_2$ 270.21

4-Isoxazolecarboxamide, 5-methyl-*N*-[4-(trifluoromethyl)-phenyl]-.

α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-*p*-toluidide. [*75706-12-6*].

» Leflunomide contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_9F_3N_2O_2$, calculated on the dried basis.

Packaging and storage—Preserve in a well-closed container. Store at a temperature not exceeding 25°.

USP Reference standards ⟨11⟩**—***USP Leflunomide RS. USP Leflunomide Related Compound A RS. USP Leflunomide Related Compound B RS. USP Leflunomide Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Dry the substance for 10 minutes at 130°.

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 165° and 168°.

Loss on drying ⟨731⟩**—**Dry it in vacuum over diphosphorus pentoxide at 60° for 4 hours. It loses not more than 0.3% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

Limit of leflunomide related compound A—

Mobile phase, System suitability preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Test solution—Transfer about 125.0 mg of Leflunomide, accurately weighed, to a 50-mL volumetric flask, dissolve in 5 mL of acetonitrile, dilute with *Mobile phase* to volume, and mix.

In-Process Revision

Standard solution—Transfer about 12.5 mg of USP Leflunomide Related Compound A RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 5 mL of acetonitrile, and dilute with *Mobile phase* to volume. Quantitatively dilute this solution with *Mobile phase* to obtain a final solution having a known concentration of about 0.25 µg per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the peak responses for leflunomide related compound A. Calculate the percentage of leflunomide related compound A in the portion of Leflunomide taken by the formula:

$$5000(C_S / W)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Leflunomide Related Compound A RS in the *Standard solution; W* is the weight, in mg, of USP Leflunomide Related Compound A RS taken to prepare the *Standard solution;* and r_U and r_S are the peak areas of leflunomide related compound A obtained from the *Test solution* and the *Standard solution,* respectively.

Chromatographic purity—

Mobile phase, System suitability preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Standard solution—Dilute a volume of the *Standard preparation,* prepared as directed in the *Assay,* with *Mobile phase* to obtain a final solution having a concentration of about 0.5 µg per mL.

System sensitivity solution—Dilute a volume of the *Standard solution* with *Mobile phase* to obtain a final solution having a concentration of about 0.25 µg per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* the *Standard solution,* and the *System sensitivity solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The signal-to-noise ratio for the peak corresponding to leflunomide in the *System sensitivity solution* is not less than 10. Disregard any peak with an area less than the leflunomide peak in the chromatogram obtained from the *System sensitivity solution.* Continue the elution for two times the retention time of the leflunomide peak. Calculate the percentage of each related compound and any unknown impurity (see *Table 1*) in the portion of Leflunomide taken by the formula:

$$5000(C_S / W)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Leflunomide RS in the *Standard solution; W* is the weight, in mg, of Leflunomide taken to prepare the *Test solution;* r_i is the peak area response for each impurity obtained from the *Test solution;* and r_S is the leflunomide peak area response obtained from the *Standard solution*.

Table 1

Name	Relative Retention Time	Response Factor	Limit (%)
5-Methylisoxazole-carboxylic acid	0.05	1.0	0.1
Leflunomide related compound B	0.22	1.0	0.3
N-(2′-Trifluoromethylphenyl)-5-methylisoxazole-4-carboxomide	0.29	1.0	0.1
2-Cyano-acetic acid-(4′-trifluoromethyl)-anilide	0.36	1.0	0.1
4-Trifluoromethyl-aniline	0.39	1.0	0.1
Leflunomide related compound C	0.94	1.0	0.1
Any other individual impurity	—	—	0.1
Total impurities, excluding leflunomide related compound B and leflunomide related compound C	—	—	0.2
Total impurities	—	—	0.4

Organic volatile impurities ⟨467⟩**:** meets the requirements.

Residual solvents ⟨467⟩**:** meets the requirements.

(Official January 1, 2007)

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and triethylamine (65 : 35 : 0.5). Adjust with phosphoric acid to a pH of 4. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Leflunomide RS in 5 mL of acetonitrile, 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.

System suitability preparation—Dissolve accurately weighed quantities of USP Leflunomide Related Compound B RS and USP Leflunomide Related Compound C RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 0.15 mg per mL and 0.05 mg per mL, respectively.

Assay preparation—Transfer about 25.0 mg of Leflunomide, accurately weighed, to a 50-mL volumetric flask, dissolve in 5 mL of acetonitrile, dilute with *Mobile phase* to volume, and mix. [NOTE—Protect solutions from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.2 for leflunomide related compound B and 0.9 for leflunomide related compound C; and the resolution, *R,* between the leflunomide and leflunomide related compound C peaks is not less than 1.0.

In-Process Revision

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 leflunomide peak. Calculate the quantity, in mg, of $C_{12}H_9F_3N_2O_2$ in the portion of Leflunomide taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Leflunomide 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 (*USP29*)

BRIEFING

Leflunomide Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Symmetry brand of L1 column. The typical retention time for leflunomide is about 28 minutes.

(PA2: C. Anthony) RTS—41078-2

Add the following:

■Leflunomide Tablets

» Leflunomide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of leflunomide ($C_{12}H_9F_3N_2O_2$).

Packaging and storage—Preserve in tight, light- and humidity-resistant containers.

USP Reference standards ⟨11⟩**—***USP Leflunomide RS. USP Leflunomide Related Compound A RS. USP Leflunomide Related Compound B RS. USP Leflunomide Related Compound C RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Spectral range: 220 to 360 nm.

Solution: 0.01 mg per mL.

Medium: methanol.

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.

PROCEDURE FOR CONTENT UNIFORMITY—

Mobile phase, Standard preparation, System suitability preparations, and *Chromatographic system*—Prepare as directed in the *Assay.*

Test solution—Transfer 1 Tablet to a suitable volumetric flask, and prepare a solution having a concentration of about 1 mg of leflunomide per mL. Add *Mobile phase* 50% by volume, and shake to disintegrate the Tablet. After the Tablet is completely disintegrated, add acetonitrile 20% by volume, dilute with *Mobile phase* to volume, and shake again. Pass through a membrane filter.

Procedure—Proceed as directed in the *Assay,* except to use the *Test solution* instead of the *Assay preparation.*

Water, *Method Ic* ⟨921⟩**:** not more than 9.0%.

Related compounds—

Mobile phase, System suitability preparations, and *Chromatographic system*—Proceed as directed in the *Assay.*

In-Process Revision

Standard solution and *Test solution*—Prepare as directed for *Standard preparation* and *Assay preparation,* respectively, in the *Assay.*

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. Calculate the percentage of each individual impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of each individual impurity in the chromatogram obtained from the *Test solution;* and r_s is the sum of all the related compounds and the leflunomide peak responses in the chromatogram obtained from the *Test solution:* not more than 0.1% of leflunomide related compound A is found; not more than 3.5% of leflunomide related compound B is found; not more than 0.1% of any other individual impurity is found; and not more than 4.0% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, and triethylamine (65 : 35 : 05), filter, and degas. Adjust with phosphoric 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 Leflunomide RS in a minimum volume of acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 mg per mL.

System suitability preparation 1—Transfer 20.0 mg of USP Leflunomide Related Compound A RS, accurately weighed, to a 20-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

System suitability preparation 2—Transfer 100.0 mg of USP Leflunomide Related Compound B RS and 10.0 mg of USP Leflunomide Related Compound C RS, each accurately weighed, to a 100-mL volumetric flask. Add 1 mL of *System suitability preparation 1,* 5 mL of acetonitrile, and 80 mL of *Mobile phase,* and shake by mechanical means for 10 minutes. Dilute with *Mobile phase* to volume, and mix.

System suitability preparation 3—Transfer about 100.0 mg of USP Leflunomide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in 2 mL of acetonitrile, add 1 mL of *System suitability preparation 2* and 80 mL of *Mobile phase,* and shake by mechanical means for 10 minutes. 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 the powder, equivalent to about 100 mg of leflunomide, to a 100.0-mL volumetric flask. Add 20 mL of acetonitrile, dilute with *Mobile phase* to volume, and shake by mechanical means for 10 minutes. Pass through a membrane filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.0-mm × 12.5-cm column containing packing L1. The flow rate is about 1 mL per minute. Chromatograph *System suitability preparation 3* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times for leflunomide related compound A, leflunomide related compound B, leflunomide related compound C, and leflunomide are about 0.4, 0.2, 0.9, and 1.0, respectively; the resolution, *R,* between leflunomide related compound C and leflunomide is not less than 1.5; the tailing factor for leflunomide is not more than 3.0; 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 leflunomide ($C_{12}H_9F_3N_2O_2$) 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 USP Leflunomide 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 (*USP29*)

BRIEFING

Lithium Carbonate Extended-Release Tablets, *USP 28* page 1142 and page 3499 of the *Second Supplement.* It is proposed to delete *Dissolution Test 3* because there are no approved products using this test. Also, it is proposed to make some changes in the *Tolerances* in *Dissolution Test 4* and to add a *Dissolution Test 5* for a new generic product recently approved by the FDA. In the absence of any adverse comments, it is proposed to implement all these revisions via the *First Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of February 1, 2006.

(BPC: M. Marques) RTS—42144-1; 42707-1

Change to read:

■**Dissolution** ⟨711⟩—■2S (*USP28*)

TEST 1—If the product complies with this test, the labeling indicates that it meets ■USP *Dissolution Test 1.*■2S (*USP28*)
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 *Medium* if necessary, and using *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 2.*■2S (*USP28*)

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 *Dissolution Test 2.*■2S (*USP28*)
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 2.*■2S (*USP28*)

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 *Dissolution Test 3.*■2S (*USP28*)~~
~~*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 2.*■2S (*USP28*)~~

~~Time (hours)~~	~~Amount dissolved~~
~~1~~	~~between 10% and 45%~~
~~2~~	~~between 25% and 75%~~
~~6~~	~~not less than 70%~~

•●1
TEST 4—If the product complies with this test, the labeling indicates that it meets ■USP *Dissolution Test 4.*■2S (*USP28*)
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 2.*■2S (*USP28*)

Time (minutes)	Amount dissolved
15	~~between 2% and 16%~~
	•not more than 15%●1
45	between 25% and 45%
90	~~between 60% and 85%~~
	•between 50% and 80%●1
120	not less than ~~80%~~
	•70%●1

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•TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: water, 900 mL.

Apparatus 1: 100 rpm.

Times: 30, 90, and 150 minutes.

Procedure—Pass a portion of the solution under test through a 0.8-µm mixed cellulose esters filter discarding the first 10 mL. Using the rest of the filtrate as the *Assay preparation,* suitably diluted with *Medium,* if necessary, and using *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 2.*

Time (minutes)	Amount dissolved
30	between 10% and 30%
90	between 55% and 75%
150	not less than 85%

•[1]

■(Official April 1, 2006)■2S (*USP28*)

BRIEFING

Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed. The procedure in the *Assay for anhydrous citric acid* is based on analyses performed with an IonPac AS11 brand of L61 column. The typical retention time for citrate is about 6 minutes. The proposal previously published in *PF* 26(4) is now being canceled.

(PA4: E. Gonikberg; NL: L. Paul; PSD: C. Okeke; AMB: R. Tirumalai) RTS—42804-1

Add the following:

■Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution

» Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution contains a dry mixture of Magnesium Carbonate, Citric Acid, and Potassium Citrate that when constituted as directed in the labeling yields a solution that contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of magnesium citrate ($C_{12}H_{10}Mg_3O_{14}$).

Packaging and storage—Preserve in tight, single-dose containers. Store at controlled room temperature.

Labeling—The label specifies the directions for the constitution of the powder and states the equivalent amount of magnesium citrate ($C_{12}H_{10}Mg_3O_{14}$).

USP Reference standards ⟨11⟩—*USP Citric Acid RS.*

Microbial limits ⟨61⟩—The total aerobic microbial count is not more than 1000 cfu per g. The total combined molds and yeasts count is not more than 100 cfu per g. It meets the requirements of the tests for absence of *Escherichia coli*.

Uniformity of dosage units ⟨905⟩**:** meets the requirements.

pH ⟨791⟩**:** between 3.3 and 4.3, determined in a solution constituted as directed in the labeling.

Other requirements—Constitute as directed in the labeling: it meets the requirements of the tests for *Identification, Chloride, Sulfate,* and *Tartaric acid* under *Magnesium Citrate Oral Solution.*

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Assay for anhydrous citric acid—

Mobile Phase and *Chromatographic System*—Proceed as directed in the general test chapter *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Standard preparation—Dissolve USP Citric Acid RS in a freshly prepared 1 mM sodium hydroxide to prepare a solution having a known concentration of about 0.02 mg of anhydrous citric acid per mL.

Assay preparation—Constitute the Oral Solution as directed in the labeling. Transfer the amount of the constituted Oral Solution, equivalent to about 500 mg of magnesium citrate, to a suitable volumetric flask, and dilute quantitatively, and stepwise if necessary, with a freshly prepared 1 mM sodium hydroxide to obtain a solution containing about 0.02 mg per mL of magnesium citrate, based on the label claim. Pass the resulting solution through a filter having a 0.5-µm or finer porosity, and use the filtrate.

Procedure—Proceed as directed for *Procedure* in *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩, and calculate the content, in g, of anhydrous citric acid ($C_6H_8O_7$) by the formula:

$$0.001(C_S\ D\ V_T\ /V)(r_U/r_S)$$

in which 0.001 is the conversion factor from mg to g; C_S is the concentration, in mg per mL, of anhydrous citric acid in the *Standard preparation; D* is the dilution factor for the *Assay preparation;* V_T is the total volume of constituted Oral Solution, as measured, when constituted as directed; V is the volume, in mL, of the constituted Oral Solution taken to prepare the *Assay preparation;* and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. The content of anhydrous citric acid is between 126.1% and 154.4% of the labeled amount of magnesium citrate.

Assay for magnesium oxide—Transfer an accurately measured volume of the constituted Oral Solution, equivalent to about 0.5 g of magnesium oxide, to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a beaker. While stirring, add 10 mL of ammonia–ammonium chloride buffer TS, 5 mL of triethanolamine, 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS until the last hint of violet disappears (blue endpoint). Each mL of 0.05M edetate disodium is equivalent to 7.520 mg of magnesium citrate ($C_{12}H_{10}Mg_3O_{14}$). ■2S *(USP29)*

BRIEFING

Megestrol Acetate Oral Suspension, *USP 28* page 1200 and page 3502 of the *Second Supplement.* It is proposed to correct the final concentration of the *Standard solution* used in *Dissolution Test 1.*

(BPC: M. Marques) RTS—42694-1

Change to read:

Dissolution ⟨711⟩—

■TEST 1—

Medium: 0.5% sodium lauryl sulfate in water; 900 mL.

Apparatus 2: 25 rpm.

Time: 30 minutes.

Standard solution—Transfer about 45 mg, accurately weighed, of USP Megestrol Acetate RS to a 250-mL volumetric flask, add about 12 mL of methanol, and put the flask in a warm water bath until the solid is dissolved. Dilute with *Medium* to volume. The final concentration is about ~~18 µg~~

■180 µg■2S *(USP29)* of megestrol acetate per mL.

Procedure—Transfer to the surface of the *Medium* in the dissolution vessel an accurately measured volume of Oral Suspension, freshly mixed and free from air bubbles, equivalent to about 160 mg of megestrol acetate. Determine the amount of $C_{24}H_{32}O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm on filtered portions of the

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solution under test, in comparison with the *Standard solution.* Calculate the percentage of megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times V \times LC}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; V* is the sample volume, in mL, of Oral Suspension taken; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.5% sodium lauryl sulfate in water; 900 mL.

Apparatus 2: 25 rpm.

Time: 30 minutes.

Standard solution—Transfer about 45 mg, accurately weighed, of USP Megestrol Acetate RS to a 250-mL volumetric flask. Add about 5 mL of methanol, and mix. Dilute with *Medium* to volume. Transfer 10 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume. The final concentration is about 18 µg per mL.

Test solution—[NOTE—Use a separate syringe for each vessel.] Withdraw more than 10 mL of the Oral Suspension, using a 10-mL syringe with a long cannula. Remove air bubbles from the syringe. Adjust the volume to the 10-mL mark on the syringe, and remove the needle. Wipe the tip of the syringe, and accurately weigh (gross weight). Operate the apparatus, and rapidly dispense the Oral Suspension to the side of the vessel at about halfway from the bottom. Similarly dispense the Oral Suspension into other vessels. Accurately weigh each syringe after dispensing the sample (tare weight). Record sample weights. After completion of the dissolution, pass an aliquot through a nylon filter having a 0.45-µm porosity, and dilute 2.0 mL of the filtrate with *Medium* to 50.0 mL to obtain a solution having a theoretical concentration of about 18 µg per mL.

Procedure—Determine the amount of $C_{24}H_{32}O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm, using 0.5-cm pathlength cuvettes, on the *Test solution* in comparison with the *Standard solution*. Calculate the percentage of megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{A_U \times C_S \times 900 \times d \times 100}{A_S \times W_U \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; d* is the density, in mg per mL, of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL; W_U is the weight, in mg, of Oral Suspension taken; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.5% sodium lauryl sulfate in degassed water; 900 mL. Use ultrapure sodium lauryl sulfate with an assay content of not less than 99.0%.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of $C_{24}H_{32}O_4$ dissolved by employing the following method.

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—Transfer about 11.5 mg, accurately weighed, of USP Megestrol Acetate RS to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Proceed as directed for *Test 2,* introducing the sample into the vessel over a 10- to 15-second period (about 1 mL per second).

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.*

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 megestrol acetate ($C_{24}H_{32}O_4$) released by the formula:

$$\frac{r_U \times C_S \times 900 \times d \times 100}{r_S \times W_U \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; d* is the density, in mg per mL, of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL; W_U is the weight, in mg, of Oral Suspension taken; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{32}O_4$ is dissolved in 30 minutes.■2S (*USP28*)

BRIEFING

Methoxyflurane, *USP 28* page 1252. It is proposed to delete the test for *Foreign odor* because it is an odor test, and there are potential safety concerns.

(PA1: K. Russo) RTS—42915-4

Delete the following:

■~~**Foreign odor**—Place 10 mL on a dry watch glass, and allow it to evaporate spontaneously to about 1 mL: no foreign odor is perceptible during the evaporation. To the remaining test specimen add a piece of odorless filter paper, and allow the paper to dry, checking it for foreign odor every few seconds during the drying period. As the last traces of odor leave the paper, a faint, characteristic odor may be detected for a few seconds, but no residual foreign odor is detected.~~■2S (*USP29*)

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BRIEFING

Miconazole Nitrate Vaginal Suppositories, *USP 28* page 1296. In the *Assay,* the *Internal standard solution, Standard preparation, Chromatographic system,* and *Procedure* are currently cross-referenced to the corresponding sections in the *Assay* under Miconazole Nitrate Cream. However, the gas chromatographic method used in the *Assay* under Miconazole Nitrate Cream has been changed to an HPLC method. Therefore, it is proposed to specify the *Internal standard solution, Standard preparation, Chromatographic system,* and *Procedure* used for the gas chromatographic procedure in the *Assay* under Miconazole Nitrate Vaginal Suppositories.

(PA7b: B. Davani) RTS—42729-1

Change to read:

Assay—

~~*Internal standard solution, Standard preparation*, and *Chromatographic system*: Prepare as directed in the *Assay* under *Miconazole Nitrate Cream*.~~

■*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 to dryness with the aid of a current of filtered air. Dissolve the residue in 2.0 mL of *Internal standard solution* to obtain a solution having a concentration of about 2500 µg per mL.■2S (*USP29*)

Assay preparation—Transfer 1 Suppository to a stoppered, 50-mL centrifuge tube. Add 30 mL of pentane, and shake by mechanical means for 20 minutes to dissolve the suppository base and to disperse the miconazole nitrate. Centrifuge to obtain a clear supernatant. Aspirate, and discard the clear liquid. Wash the residue with three 20-mL portions of pentane, shaking, centrifuging, and aspirating in the same manner. Discard the pentane washings. Evaporate the residual pentane from the residue with the aid of a current of filtered air. Using small portions of methanol, transfer the residue to a 100-mL volumetric flask. Dissolve in methanol, dilute with methanol to volume, and mix. Transfer an accurately measured volume of this stock solution, equivalent to about 5 mg of miconazole nitrate, to a suitable container, and evaporate to dryness on a steam bath with the aid of a current of filtered air. 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 carrier gas is helium, flowing at a rate of about 50 mL per minute. The injection port, detector, and column temperatures are maintained at about 250°, 300°, and 250°, respectively. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times for cholestane and miconazole nitrate are about 0.44 and 1.0, respectively; 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%.■2S (*USP29*)

Procedure—~~Proceed as directed for *Procedure* in the *Assay* under *Miconazole Nitrate Cream*.~~

■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.■2S (*USP29*)

Calculate the quantity, in mg, of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) in the portion of Suppository taken by the formula:

$$(0.2C/V)(R_U/R_S)$$

in which ~~*V* is the volume, in mL, of stock solution used to prepare the Assay preparation, and the other terms are as defined therein.~~

■*C* is the concentration, in µg per mL, of the USP Miconazole Nitrate RS in the *Standard preparation; V* is the volume, in mL, of stock solution used to prepare the *Assay preparation;* and R_U and R_S are the ratios of the peak responses of miconazole nitrate to that of cholestane obtained from the *Assay preparation* and *Standard preparation,* respectively.■2S (*USP29*)

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BRIEFING

Norgestimate, *USP 28* page 1401. It is proposed to add system suitability requirements to *Test 1* of the tests for *Chromatographic purity* and to revise *USP Reference standards* by adding the associated Reference Standards. In the test for *Limit of residual solvents,* it is proposed to add requirements for *Option 1* and *Option 2* from general chapter ⟨467⟩. Minor changes in the *Assay* are also proposed.

(PA1: C. Anthony) RTS— 42976-1

Change to read:

USP Reference standards ⟨11⟩—*USP Norgestimate RS.*

■*USP Norgestimate Related Compound A RS. USP Norgestimate Oxime Mixture RS.*■2S (*USP29*)

Change to read:

Limit of residual solvents ⟨467⟩—

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 of *Internal standard solution* and 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.

■*Option 1:* not■2S (*USP29*)
more than 0.5% each of acetone and alcohol is found, not more than 0.05% of diisopropyl ether is found, not more than 0.006% of chloroform is found, and not more than 0.3% of methanol is found;

■or *Option 2:* meets the requirements.■2S (*USP29*)

Change to read:

Chromatographic purity—

TEST 1—

Diluent, Mobile phase, ~~*System suitability solution,*~~

■*Sensitivity solution,*■2S (*USP29*)
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.*

■*System suitability solution*—Dissolve accurately weighed quantities of USP Norgestimate RS, USP Norgestimate Related Compound A RS and USP Norgestimate Oxime Mixture RS in *Diluent* to obtain a solution containing about 0.5 mg per mL of each.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 244-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. 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 relative retention times are about 0.50 for syn-17-deacetyl norgestimate, about 0.56 for anti-17-deacetyl norgestimate, about 0.72 for norgestimate related compound A, and 1.0 for norgestimate; the resolution, *R,* between syn-17-deacetyl norgestimate and anti-17-deacetyl norgestimate is not less than 1.5; and that between anti-17-deacetyl norgestimate and norgestimate related compound A is not less than 1.5.■2S (*USP29*)

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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;~~

■for each impurity;■2S (*USP29*)
and r_S is the peak area of *(E)*-norgestimate,

■eluting at about 13.5 minutes,■2S (*USP29*)
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.~~

■The impurities meet the requirements specified in the table below.

Impurities	Relative Response Time	Relative Response Factor	Limit (not more than)
syn-17-Deacetyl norgestimate*	0.50	0.83	0.3
anti-17-Deacetyl norgestimate*	0.56	1.13	0.3
Norgestimate related compound A (levonorgestrel acetate)	0.72	0.85	0.3%
Any other impurity	—	1.0	0.1%

* Provided as a mixture called USP Norgestimate Oxime Mixture RS; their combined limits are not more than 0.3%.■2S (*USP29*)

TEST 2—
Mobile phase—Prepare a filtered and degassed mixture of cyclohexane and absolute 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 the *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 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 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 is found. Not more than 1.0% of total impurities is found, the results for *Test 1* and *Test 2* being added.

Change to read:

Assay—
Diluent—Prepare a mixture of methanol and water (4 : 1).
Mobile phase—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and acetonitrile (30 : 11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard preparation—Dissolve an accurately weighed quantity of USP Norgestimate RS in *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.
~~*System suitability solution*—~~

■*Sensitivity solution*—■2S (*USP29*)
Dilute a portion of *Standard preparation,* quantitatively and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.05 µg per mL.
Assay preparation—Transfer about 25 mg of Norgestimate, 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 244-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The

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flow rate is about 1.2 mL per minute. The column temperature is maintained at about 40°. Chromatograph the ~~*System suitability solution,*~~

■*Sensitivity solution,*■2S *(USP29)* and record the peak areas as directed for *Procedure:* the signal-to-noise ratio for *(Z)*-norgestimate is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.86 for *(Z)*-norgestimate and 1.0 for *(E)*-norgestimate; the resolution, *R,* between *(Z)*-norgestimate and *(E)*-norgestimate is not less than 1.5; the tailing factor for *(E)*-norgestimate and for *(Z)*-norgestimate is not more than 1.5; and the relative standard deviation for replicate injections, determined from the peak area ratio of *(E)*-norgestimate to *(Z)*-norgestimate, 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 areas for the major peaks. Calculate the quantity, in mg, of $C_{23}H_{31}NO_3$ in the portion of Norgestimate taken by the formula:

$$50C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard preparation;* and r_U and r_S are the sums of the peak areas of *(Z)*-norgestimate and *(E)*-norgestimate obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the percentages of the *(Z)*- and *(E)*-isomers, U_Z and U_E, respectively, in the portion of Norgestimate taken by the formula:

$$5000(CP/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard preparation; P* is the fraction of *(E)*- or *(Z)*-norgestimate in USP Norgestimate RS; *W* is the weight, in mg, of Norgestimate taken to prepare the *Assay preparation;* and r_U and r_S are the peak responses of the appropriate norgestimate isomer obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the ratio of *(E)*-norgestimate to *(Z)*-norgestimate, that is, the ratio of U_E to U_Z.

BRIEFING

Omeprazole Delayed-Release Capsules, *USP 28* page 1417 and page 3514 of the *Second Supplement.* On the basis of comments received, it is proposed to delete *Identification* test *A.* The remaining identification test, based on the HPLC retention time agreement of the major peak in the *Assay preparation* and the *Standard preparation,* is capable of identifying the active ingredient in this drug product and does not require supplementation by the TLC test. It is also proposed to add chemical names for impurities under the test for *Chromatographic purity.*

(PA4: E. Gonikberg) RTS—42576-1

Change to read:

Identification—

~~**A:** *Thin Layer Chromatographic Identification Test* ⟨201⟩—~~

~~*Adsorbent:* 0.25-mm chromatographic silica gel mixture, prewashed with methanol.~~

~~*Diluent:* a mixture of methylene chloride and methanol (1 : 1).~~

~~*Test solution* Transfer the contents of not fewer than 5 Capsules to a mortar, grind the Capsules, and mix. Transfer a weighed quantity of the powder, equivalent to about 10 mg of omeprazole, to a suitable container. Add 2 mL of *Diluent,* sonicate for 5 minutes, and allow to settle for 20 minutes before applying to the plate.~~

~~*Standard solution* Dissolve an accurately weighed quantity of USP Omeprazole RS in *Diluent* to obtain a solution having a known concentration of about 5 mg per mL.~~

~~*Developing solvent system:* a mixture of methylene chloride saturated with ammonia, methylene chloride, and isopropyl alcohol (2 : 2 : 1).~~

~~**B:**~~

■■2S *(USP29)*

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:

Chromatographic purity—

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

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

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 all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

~~$(10C/FA)(r_i/r_S)$~~

■$10(C/A)(1/F)(r_i/r_S)$■2S *(USP29)*

in which C is the concentration, in µg per mL, of USP Omeprazole RS in the *Standard solution; A* is the quantity, in mg, of omeprazole in the portion of Capsules taken, as determined in the *Assay; F* is the relative response factor (see ~~*Note*~~

■*Table 1*■2S *(USP29)* below for values); r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for omeprazole obtained from the *Standard solution.* ~~not more than 0.5% of any individual impurity is found, and~~

■In addition to not exceeding the limits for each impurity in *Table 1,*■2S *(USP29)* not more than 2.0% of total impurities is found. ~~[NOTE—The relative response factor, *F,* equals 1.6 and 3.1 for peaks with a relative retention time of about 0.33 and 0.64, respectively; and equals 1.0 for peaks obtained from all other impurities.]~~

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■**Table 1**

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Thioxopyrido conversion product[1]	0.33	1.6	0.5
5-methoxy-1*H*-benzimidazole-2-thiol	0.64	3.1	0.5
Any other individual impurity	—	1.0	0.5

[1] Formed in the solution from two isomers: 1,3-dimethyl-8-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one and 1,3-dimethyl-9-methoxy-12-thioxopyrido[1′,2′:3,4]imidazo[1,2-*a*]benzimidazol-2(12*H*)-one.■2S (*USP29*)

BRIEFING

PEG 3350 and Electrolytes for Oral Solution, *USP 28* page 1575. It is proposed to change the official title of this monograph to Polyethylene Glycol 3350 and Electrolytes for Oral Solution. In accordance with the procedures of the USP Nomenclature and Labeling Expert Committee, the term "PEG" is not appropriate for official titles; the proposed revision eliminates its use. In addition, minor editorial style changes have been made. In the absence of any significant adverse comments, the revision to the official title will appear in the *Second Supplement to USP 29–NF 24,* but with a delayed implementation date of **February 1, 2009**.

(PA1: K. Russo; NL: L. Paul) RTS—42914-1

Change to read:

~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP29*)

(Title for this monograph—to become official February 1, 2009). (Prior to February 1, 2009, the current practice of labeling the article of commerce with the name PEG 3350 and Electrolytes for Oral Solution may be continued).

Change to read:

» ~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP29*)
is a mixture of Polyethylene Glycol 3350, Sodium Bicarbonate, Sodium Chloride, Sodium Sulfate (anhydrous), and Potassium Chloride. When constituted as directed in the labeling, it contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of polyethylene glycol 3350, potassium (K^+), sodium (Na^+), bicarbonate (HCO_3^-), chloride (Cl^-), and sulfate (SO_4^{-2}), the labeled amounts per L being 10 mmol (10 mEq) of potassium, 125 mmol (125 mEq) of sodium, 20 mmol (20 mEq) of bicarbonate, 35 mmol (35 mEq) of chloride, and 40 mmol (80 mEq) of sulfate.

Change to read:

Assay for potassium and sodium—

Mobile phase—Dilute 0.5 mL of nitric acid with water to obtain 4000 mL of solution. Degas, and place the solution in a suitable plastic container. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve a suitable quantity of ammonium bromide in water to obtain a solution having a concentration of about 2 mg per mL.

Standard preparation—To a 100-mL volumetric flask transfer about 90 mg of potassium chloride, previously dried at 105° for 2 hours and accurately weighed, and about 880 mg of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 500-mL volumetric flask, add 10.0 mL of *Internal standard solution,* dilute with water to volume, and mix. Pass this solution through a filter having a 0.5-µm or finer porosity, and store the filtrate in a suitable plastic container. This *Standard preparation* contains about 9 µg (0.00012 mEq) of potassium chloride and about 88 µg (0.0015 mEq) of sodium chloride per mL.

Assay preparation—Constitute the contents of a container of ~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP29*)

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with an accurately measured volume of water, as specified in the labeling. Transfer 6.0 mL of this stock solution, equivalent to about 0.06 mEq of potassium, to a 500-mL volumetric flask, add 10 mL of *Internal standard solution*, dilute with water to volume, and mix. This solution contains about 0.00012 mEq of potassium and 0.0015 mEq of sodium per mL. [NOTE—Reserve the remaining portion of the stock solution for the *Assay for bicarbonate*, and reserve the remaining portion of the *Assay preparation* for the *Assay for chloride and sulfate* and the *Assay for polyethylene glycol 3350*.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector, a 4-mm × 5-cm guard column containing packing L22, and a 4-mm × 30-cm analytical column maintained at 35 ± 1° containing packing L22. The flow rate is about 0.9 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the relative retention times are about 0.6 for sodium, 0.8 for ammonium, and 1.0 for potassium; and the resolution, *R,* between sodium and ammonium is not less than 1.1 and the resolution, *R,* between ammonium and potassium is not less than 0.9. [NOTE—Maintain column backpressure at less than 1000 pounds per square inch. Backpressure may be reduced by changing the in-line filters and frits in the columns. Column efficiency may be improved by backflushing the analytical column with 30 mL of 0.1 N nitric acid or by injecting four successive 100-µL portions of 0.1 N nitric acid into the chromatograph.]

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 area responses for the major peaks. Calculate the mEq of potassium per L of constituted Oral Solution taken by the formula:

$$(500 / 74.55)(C / 6)(R_U / R_S)$$

in which 74.55 is the molecular weight of potassium chloride; C is the concentration, in µg per mL, of potassium chloride in the *Standard preparation;* and R_U and R_S are the peak area response ratios of potassium to ammonium obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the mEq of sodium per L of constituted Oral Solution taken by the formula:

$$(500 / 58.44)(C / 6)(R_U / R_S)$$

in which 58.44 is the molecular weight of sodium chloride; C is the concentration, in µg per mL, of sodium chloride in the *Standard preparation;* and R_U and R_S are the peak area response ratios of sodium to ammonium obtained from the *Assay preparation* and the *Standard preparation,* respectively.

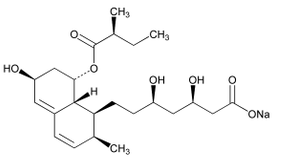
BRIEFING

Pravastatin Sodium. 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 procedures in the test for *Chromatographic purity* are based on analyses performed with the 3.5-µm Zorbax SB C18 brand of L1 column. Alternatively, the 3-µm Hypersil ODS brand of L1 column can be used for this test. The typical retention time for pravastatin is about 8 minutes. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the 3-µm Hypersil ODS brand of L1 column. The typical retention time for pravastatin is 7 minutes. The gas chromatographic procedures in the test for *Limit of alcohol* are based on the analyses performed with the Supelco OVI-G43 brand of G43 column.

(PA4: E. Gonikberg; NL: L. Paul) RTS—36919-1

Add the following:

■Pravastatin Sodium



$C_{23}H_{35}NaO_7$ 446.51

1-Napththaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1*S*-[1α(β*S**,δ*S**),2α,6α,8β(*R**),8aα]]-.

Sodium (β*R*,δ*R*,1*S*, 2*S*,6*S*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-β,δ,6,8-tetrahydroxy-2-methyl-1-naphthaleneheptanoate, 8-[(2*S*)-2-methylbutyrate] [*81131-70-6*].

» Pravastatin Sodium contains not less than 98.0 percent and not more than 102.0 percent of $C_{23}H_{35}NaO_7$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in tight containers. Store under nitrogen in a cold place.

USP Reference standards ⟨11⟩**—***USP Pravastatin Sodium RS. USP Pravastatin Related Compound A RS.*

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Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the pyroantimonate precipitation test for *Sodium* ⟨191⟩.

Specific rotation ⟨781⟩**:** between +150° and +160° (at 20°), calculated on the anhydrous and solvent-free basis.

Test solution: 5 mg per mL in water.

pH ⟨791⟩**:** between 7.2 and 9.0, in a solution (1 in 20).

Water, *Method I* ⟨921⟩**:** not more than 4.0%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Chromatographic purity—[NOTE—The *Standard solution* and the *Test solution* are maintained at 15° until injected into the chromatograph.]

Diluent—Prepare a mixture of methanol and water (1 : 1).

Buffer pH 7.0—Prepare a 0.08 M phosphoric acid solution, adjust with triethylamine to a pH of 7.0, and mix.

Solution A—Prepare a filtered and degassed mixture of water, *Buffer pH 7.0,* and acetonitrile (52 : 30 : 18).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, *Buffer pH 7.0,* and water (60 : 30 : 10).

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 Pravastatin Sodium RS in *Diluent,* 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 accurately weighed quantities of USP Pravastatin Sodium RS and USP Pravastatin Related Compound A RS in *Diluent* to obtain a solution containing about 0.5 mg of USP Pravastatin Sodium RS and 0.001 mg of USP Pravastatin Related Compound A RS per mL. [NOTE—USP Pravastatin Related Compound A RS is a sodium salt of 6α-hydroxyisocompactin acid.]

Test solution—Transfer about 50 mg of Pravastatin Sodium, 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 238-nm detector and a 4.6-mm × 7.5-cm column that contains 3.5-µm packing L1. Alternatively, a 4.0-mm × 10-cm column that contains 3-µm packing L1 can be used. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3.0	100	0	isocratic
3.0–26.5	100→0	0→100	linear gradient
26.5–26.6	0→100	100→0	linear gradient
26.6–30.0	100	0	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 1.0 for pravastatin and 1.1 for pravastatin related compound A; and the resolution, *R,* between pravastatin and pravastatin 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 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into a chromatograph, record the chromatograms, identify the impurities listed in *Table 1,* and measure the peak responses.

Calculate the percentage of each impurity in the portion of Pravastatin Sodium taken by the formula:

$$100C(V/W)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Pravastatin Sodium RS in the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of Pravastatin Sodium 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 pravastatin peak response obtained from the *Standard solution*. In addition to not exceeding the limits for each impurity specified in *Table 1,* not more than 0.1% of any other individual impurity is found, and not more than 0.6% of total impurities is found.

Table 1

Name	Relative Retention Time	Limit (%)
3″-Hydroxypravastatin	0.33	0.2
6′-Epipravastatin	0.92	0.3
6α-Hydroxyisocompactin[1]	1.1	0.2
Pentanoyl impurity[2]	1.2	0.2
Pravastatin lactone	1.8	0.2
Compactin	3.1	0.2

[1] USP pravastatin related compound A.
[2] (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylpentanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoic acid.

Limit of alcohol *(if present)*—

Standard solution—Pipet 2 mL of dehydrated alcohol into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 1 mL of this solution into a vial fitted with a septum and a crimp cap, and calculate the amount of alcohol, W_A, added, in g, the specific gravity of dehydrated alcohol being 0.79 g per mL. Add 5 mL of the *Test solution* to the same vial, seal the vial, and mix. Heat the sealed vial at 80° for 60 minutes.

Test solution—Transfer about 0.2 g of Pravastatin Sodium, accurately weighed, to a 20-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a vial fitted with a septum and a crimp cap, add 1 mL of water, seal the vial, and mix. Heat the sealed vial at 80° for 60 minutes.

Blank solution—Pipet 6 mL of water into a vial fitted with a septum and a crimp cap, and seal the vial. Heat the sealed vial at 80° for 60 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m fused silica capillary column coated with a 3-µm film of stationary phase G43. The carrier gas is helium, with a split ratio of 1 : 5, and flowing with a linear velocity of about 35 cm per second. The chromatograph is programmed as follows. The column temperature is maintained at 40° for 20 minutes, then the temperature is increased at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The transfer line temperature is maintained at 85°, the injection port temperature is maintained at 140°, and the detector is maintained at 250°. Chromatograph the *Blank solution,* and record the peak responses as directed for *Procedure:* no interfering peaks are observed.

Procedure—Separately inject equal volumes (about 1 mL) of headspace gas of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms,

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and measure the area responses for the major peaks. Calculate the percentage (w/w) of alcohol in the portion of Pravastatin Sodium taken by the formula:

$$100\ (W_A / W)(V/5)[r_U / (r_S - r_U)]$$

in which W_A is as defined above; W is the weight, in g, of Pravastatin Sodium taken to prepare the *Test solution;* V is the volume, in mL, of the *Test solution;* 5 is the volume, in mL, of the *Test solution* taken; and r_U and r_S are the peak area responses of alcohol obtained from the *Test solution* and the *Standard solution,* respectively: not more than 3.0% is found.

Assay—

Solution A—Prepare a 0.05 M phosphoric acid solution, adjust with a 25% sodium hydroxide solution to a pH of 5.0, mix, filter, and degas.

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⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Pravastatin Sodium RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.2 mg per mL.

System suitability preparation—Dissolve accurately weighed quantities of USP Pravastatin Sodium RS and USP Pravastatin Related Compound A RS in methanol to obtain a solution containing about 0.2 mg of USP Pravastatin Sodium RS and 0.001 mg of USP Pravastatin Related Compound A RS per mL.

Assay preparation—Transfer about 20 mg of Pravastatin Sodium, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 238-nm detector and a 4.0-mm × 10-cm column that contains 3-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
0–7.0	80→72	20→28	linear gradient
7.0–10.0	72→50	28→50	linear gradient
10.0–17.0	50	50	isocratic
17.0–17.1	50→80	50→20	linear gradient
17.1–20.0	80	20	re-equilibration

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for pravastatin and 1.2 for pravastatin related compound A; the resolution, *R,* between pravastatin and pravastatin related compound A is not less than 1.2; and the relative standard deviation for replicate injections for the pravastatin peak 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 pravastatin peaks. Calculate the quantity, in mg, of $C_{23}H_{35}NaO_7$ in the portion of Pravastatin Sodium taken by the formula:

$$VC(r_U / r_S)$$

in which V is the volume, in mL, of the *Assay preparation;* C is the concentration, in mg per mL, of USP Pravastatin Sodium RS in the *Standard preparation;* and r_U and r_S are the responses of the pravastatin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP29*)

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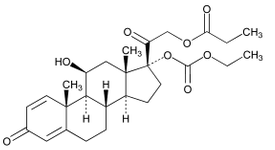
BRIEFING

Prednicarbate. Because there is no existing *USP* monograph for this drug product, a new monograph is proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the Zorbax C8 brand of L7 column. Typical retention times are about 17 minutes for prednicarbate and about 19 minutes for prednicarbate related compound A.

(PA1: C. Anthony) RTS—42709-1

Add the following:

■Prednicarbate



$C_{27}H_{36}O_8$ 488.57

(1) Pregna-1,4-diene-3,20-dione, 17-[(ethoxycarbonyl) oxy]-11-hydroxy-21-(1-oxopropoxy)-, (11*β*)-.

(2) 11*β*,17,21-Trihydroxypregna-1,4-diene-3,20-dione 17-(ethyl carbonate) 21-propionate [*73771-04-7*].

» Prednicarbate contains not less than 97.0 percent and not more than 102.0 percent of $C_{27}H_{36}O_8$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Prednicarbate RS. USP Prednicarbate 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.*

Specific rotation ⟨781S⟩**:** between +60° and +66°.

Test solution: 10 mg per mL, in alcohol.

Loss on drying ⟨731⟩—Dry it at 105° for 6 hours: it loses not more than 0.5% of its weight.

Chromatographic purity—

Mobile phase, System suitability solution, and *Chromatographic system*—Prepare as directed in the *Assay.*

Test preparation—Use the *Assay preparation*.

Diluted test preparation—Transfer 1 mL of the *Test preparation* to a 200-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes, about 20 µL of the *Test preparation* and the *Diluted test preparation,* into the chromatograph, record the chromatograms, and measure the response for the prednicarbate peak obtained from the *Diluted test preparation.* Obtain from the *Test preparation* the peak responses for prednicarbate related compound A and for all peaks other than prednicarbate. Continue the chromatography for twice the retention time of prednicarbate. Calculate the percentage of the related compound and all the impurities in the portion of Prednicarbate taken by the formula:

$$0.5(R_T / R_{DT})$$

in which R_T is the peak response for each individual impurity peak obtained from the *Test preparation,* and R_{DT} is the peak response of the main peak in the chromatogram of the *Diluted test preparation:* not more than 1.0 percent of prednicarbate related compound A is found; not more than 0.5 percent of any other individual impurity is found, with the

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exception of the main peak and the peak corresponding to prednicarbate related compound A; and not more than 2.0 percent of total impurities is found. Disregard any peak (0.0125%) with an area less than 0.025 times the area of the main peak in the chromatogram obtained with the *Diluted test solution*.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (60 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of USP Prednicarbate Related Compound A RS and Prednicarbate in *Mobile phase* to obtain a solution containing about 3 µg per mL each. [NOTE—Prepare all solutions just prior to use.]

Standard preparation—Dissolve an accurately weighed quantity of USP Prednicarbate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer about 30 mg of Prednicarbate, 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 243-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 0.7 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 1.1 for USP Prednicarbate Related Compound A RS and 1.0 for USP Prednicarbate RS; the resolution, *R,* between Prednicarbate and USP Prednicarbate Related Compound A RS is not less than 3.0.

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 responses for the prednicarbate peaks. Continue the chromatography for twice the retention time of prednicarbate. Calculate the quantity, in mg, of $C_{27}H_{36}0_8$ in the portion of Prednicarbate taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Prednicarbate 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 *(USP29)*

BRIEFING

Oral Rehydration Salts, *USP 28* page 1708, page 3531 of the *Second Supplement,* and page 445 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to delete *Identification* test *F* because it is an odor test, and there are potential safety concerns.

(PA1: K. Russo) RTS—42915-5

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Citric Acid RS.* ▲*USP29*

(Official January 1, 2009)

Change to read:

Identification—

A: It responds to the flame tests for *Sodium* ⟨191⟩ and for *Potassium* ⟨191⟩.

B: It responds to the tests for *Chloride* ⟨191⟩.

C: Where it contains Sodium Bicarbonate, it dissolves with effervescence, and the collected gas so obtained responds to the test for *Bicarbonate* ⟨191⟩.

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D: Where it contains Sodium Citrate, it responds to the tests for *Citrate* ⟨191⟩, 3 to 5 drops of the solution constituted as directed in the labeling and 20 mL of the mixture of pyridine and acetic anhydride being used.

E: Where it contains Dextrose, add a few drops of the solution constituted as directed in the labeling to 5 mL of hot alkaline cupric tartrate TS: a copious red precipitate of cuprous oxide is formed *(presence of dextrose).*

~~**F:** When heated it melts, swells, and burns, yielding the odor of burnt sugar.~~

■■2S (*USP29*)

Change to read:

Assay for citrate *(if present)*—

~~*Mobile phase*—Dissolve 20 g of ammonium sulfate in a mixture of water and acetonitrile (980 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of sodium citrate, previously dried at 180° for 18 hours, in water to obtain a solution having a known concentration of about 2.5 mg of anhydrous sodium citrate per mL.~~

~~*Assay preparation*—Transfer an accurately measured volume of the stock solution remaining from the *Assay for dextrose*, equivalent to about 180 mg of citrate ($C_6H_5O_7^{-3}$), to a 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.8-mm × 20-cm column that contains packing L8. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak response as directed for *Procedure:* the retention time for the citrate peak is about 3 minutes, 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%. [NOTE—The column may be equilibrated before use by making a series of injections of the *Standard preparation* over a period of several hours. If the tailing factor is greater than 2, the equilibration may be facilitated by adding 1 g of sodium citrate to each 1000 mL of the *Mobile phase* and pumping this solution through the column at about 0.5 mL per minute for several hours. The column must then be washed with *Mobile phase* for a few minutes before use.]~~

~~*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 $C_6H_5O_7^{-3}$ in the unit-dose container or containers taken or in the portion of powder taken from the multiple-unit container by the following formula:~~

~~$$(189.12/258.07)(10{,}000C/v)(r_U/r_S),$$~~

~~in which 189.12 and 258.07 are the molecular weights of citrate ($C_6H_5O_7^{-3}$) and anhydrous sodium citrate, respectively, C is the concentration, in mg per mL, of anhydrous sodium citrate in the *Standard preparation,* v is the volume, in mL, of the stock solution taken to prepare the *Standard preparation,* and r_U and r_S are the citrate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

▲*Mobile phase, Standard Preparation 1,* and *Chromatographic System*—Proceed as directed under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Assay preparation—Transfer an accurately measured volume of the stock solution remaining from the *Assay for dextrose*, equivalent to about 180 mg of citrate ($C_6H_5O_7$), to a suitable volumetric flask, and proceed as directed for *Assay Preparation for Citric Acid/Citrate Assay* under *Assay for Citric Acid/Citrate and Phosphate* ⟨345⟩.

Procedure—Proceed as directed for *Procedure* in ⟨345⟩. Calculate the quantity, in mg, of citrate ($C_6H_5O_7$) in the portion of Oral Rehydration Salts taken by the formula:

$$0.001C_S D(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of citrate in *Standard Preparation 1; D* is the dilution factor; and r_U and r_S are the citrate peak areas obtained from the *Assay preparation* and *Standard Preparation 1,* respectively.▲*USP29*

(Official January 1, 2009)

BRIEFING

Saquinavir Mesylate, *USP 28* page 1752. On the basis of new data received, it is proposed to provide more information on the UV in *Identification* test *B* to correspond to NDA submission.

(PA7b: B. Davani) RTS—43017-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 12 µg per mL.

Medium: methanol.

■The absorptivity of the sample preparation at 238 nm ±2 nm, calculated on the anhydrous basis, is between 61.0 and 63.4.■2S (*USP29*)

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C: 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.*

BRIEFING

Sodium Bicarbonate Injection, *USP 28* page 1778. It is proposed to revise the *Packaging and storage* statement to include the use of plastic containers. Storage conditions have also been added.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—42721-1

Change to read:

Packaging and storage—Preserve in single-dose ~~containers, of Type I glass~~

■glass or plastic containers. Glass containers are preferably of Type I glass. Store at controlled room temperature.■2S (*USP29*)

BRIEFING

Sodium Chloride, *USP 28* page 1779 and page 795 of *PF* 31(3) [May–June 2005]. In order to align the monograph with the harmonization text presented by the Pharmacopeial Discussion Group, it is proposed to revise the test for *Limit of phosphates* to include solution information from the harmonization draft.

(PA1: J. Lane) RTS—42831-1

Change to read:

Identification—~~It responds to the tests for *Sodium* ⟨191⟩ and for *Chloride.*~~

■**A:** Dissolve in 2 mL of water a quantity of the substance to be examined equivalent to about 2 mg of chloride. Acidify with diluted nitric acid, and add 0.4 mL of a silver nitrate solution containing about 42.5 g per L. Shake, and allow to stand. A curdled white precipitate is formed. Centrifuge, and wash the precipitate with three quantities, each 1 mL, of water. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in 2 mL of water, and add 1.5 mL of ammonium hydroxide. The precipitate dissolves easily with the possible exception of a few large particles that dissolve slowly.

B: Introduce into a test tube a quantity of the substance to be examined equivalent to about 15 mg of chloride. Add 0.2 g of potassium dichromate and 1 mL of sulfuric acid. Place a filter-paper strip impregnated with 0.1 mL of *Diphenylcarbazide solution* over the opening of the test tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

Diphenylcarbazide solution—Dissolve 0.2 g of diphenylcarbazide in 10 mL of glacial acetic acid, and dilute with alcohol to 100 mL. Prepare immediately before use.

C: Dissolve 0.1 g of the substance to be examined in 2 mL of water. Add 2 mL of a 150 g per L solution of potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of *Potassium pyroantimonate solution,* and heat to boiling. Allow to cool in iced water, and if necessary rub the inside of the test tube with a glass rod. A dense white precipitate is formed.

Potassium pyroantimonate solution—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly, and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution containing 8.5 g of sodium hydroxide in 100 mL of water. Allow to stand for 24 hours, filter, and dilute with water to 150 mL.

D: Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium in 0.5 mL of water. Add 1.5 mL of *Methoxyphenylacetic reagent,* and cool in ice water for 30 minutes. A voluminous, white, crystalline precipitate is formed. Place in water at 20°, and stir for 5 minutes. The precipitate does not disappear. Add 1 mL of ammonia TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution (158 g per L). No precipitate is formed.

Methoxyphenylacetic reagent—Dissolve 2.7 g of methoxyphenylacetic acid in 6 mL of 10% tetramethylammonium hydroxide solution in methanol, and add 20 mL of alcohol. Store in a polyethylene container.■1S (*USP29*)

Change to read:

Loss on drying ⟨731⟩—Dry the test material at 105° for 2 hours: it loses not more than 0.5% of its weight, determined on ~~a 1.000-g sample.~~

■about 1.000 g of sample.■1S (*USP29*)

Change to read:

Limit of phosphates—

Phosphate stock standard solution—Dissolve an accurately weighed quantity of monobasic potassium phosphate in water to obtain a solution having a concentration of about 0.716 mg per mL.

Phosphate standard solution—Dilute 1 mL of the *Phosphate stock standard solution* with water to 100 mL. Prepare this solution fresh.

Standard solution—Dilute 2 mL of the *Phosphate standard solution* with water to 100 mL.

Test solution—Dilute 2 mL of the solution prepared in the test for *Appearance of solution* with water to 100 mL.

Procedure—To the *Standard solution* and the *Test solution,* add 4 mL of ~~sulfomolybdic acid TS,~~

■*Sulfomolybdic acid solution,*■2S (*USP29*) and add 0.1 mL of a mixture of 1 mL of stronger acid stannous chloride TS and 10 mL of 2 N hydrochloric acid. After 10 minutes, compare the colors of 20 mL of each solution: any color in the *Test solution* is not more intense than that in the *Standard solution* (0.0025%).

■*Sulfomolybdic acid solution*—Dissolve with heating 2.5 g of ammonium molybdate in 20 mL of water. Dilute 28 mL of sulfuric acid with 50 mL of water, then cool. Mix the two solutions, and dilute with water to 100 mL.■2S (*USP29*)

Change to read:

Limit of potassium (where it is labeled as intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)—

Test solution—Transfer 1.00 g of Sodium Chloride to a 100-mL volumetric flask, add water and swirl to dissolve, dilute with water to volume, and mix.

Standard solution—[NOTE—The *Standard solution* and the *Test solution* may be modified, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument.] Dissolve 1.144 g of potassium chloride, previously dried at 105° for 3 hours, in water; dilute with water to 1000 mL; and mix. This solution contains the equivalent of 600 µg of potassium per mL. Dilute as required to obtain not fewer than three solutions at concentrations that span the expected value in the *Test solution*.

Procedure—Using atomic ~~absorption~~

■emission■1S (*USP29*) spectrophotometry (see *Spectrophotometry and Light-Scattering* ⟨851⟩), measure, at least three times, the emission intensity of the *Test solution* and the *Standard solution* using an air–acetylene flame and a wavelength of 766.5 nm. Prepare a calibration curve from the mean of the readings obtained with the *Standard solution,* and determine the concentration of potassium in the *Test solution:* not more than 0.05% is found.

BRIEFING

Sodium Lactate Injection, *USP 28* page 1787. It is proposed to delete *Identification* test *B* because it is an odor test, and there are potential safety concerns.

(PA1: K. Russo) RTS—42915-6

Change to read:

Identification—

~~**A:** Overlay 2 mL of Injection on 5 mL of a 1 in 100 solution of catechol in sulfuric acid: a deep red color is produced at the zone of contact.~~

~~**B:** To 2 mL of Injection add 5 mL of 2 N sulfuric acid and 2 mL of potassium permanganate TS, and heat: the odor of acetaldehyde is evolved.~~

■Overlay 2 mL of Injection on 5 mL of a 1 in 100 solution of catechol in sulfuric acid: a deep red color is produced at the zone of contact.■2S (*USP29*)

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BRIEFING

Sodium Phosphates Rectal Solution, *USP 28* page 1792. It is proposed to add a blank determination to the *Assay,* to be consistent with USP general chapter *Titrimetry* ⟨541⟩. This change will also affect the *Assay* under *Sodium Phosphates Oral Solution*.

(PA4: E. Gonikberg) RTS—42990-1

Change to read:

Assay—Pipet 5.0 mL of Rectal Solution into a 250-mL beaker, and add 15.0 mL of 0.5 N sodium hydroxide VS and 95 mL of water. Titrate the excess base potentiometrically with 0.5 N hydrochloric acid VS to the first inflection point, at a pH of about 9.2. Record the volume, *A,* in mL, of 0.5 N hydrochloric acid consumed. Continue the titration to the second inflection point, at a pH of about 4.4, and record the total volume, *B,* in mL, of 0.5 N hydrochloric acid required in the titration.

■For a blank determination, transfer 15.0 mL of 0.5 N sodium hydroxide into a 250-mL beaker, add 100 mL of water, and immediately titrate potentiometrically with 0.5 N hydrochloric acid VS. Record the volume, *C,* in mL, of 0.5 N hydrochloric acid consumed.■2S *(USP29)*
Each mL of the volume ~~(15.0 − *A*)~~

■$(C - A)$■2S *(USP29)*
of 0.5 N hydrochloric acid is equivalent to 69.0 mg of monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$). Each mL of the volume ~~(*B* − 15.0)~~

■$(B - C)$■2S *(USP29)*
of 0.5 N hydrochloric acid is equivalent to 134.0 mg of dibasic sodium phosphate ($Na_2HPO_4 \cdot 7H_2O$).

BRIEFING

Stavudine Capsules, page 3275 of the *First Supplement.* In the *Assay,* it is proposed to specify the *Standard preparation* in terms of concentration of the Reference Standard rather than specifying the exact quantity, in mg, of Reference Standard needed. This proposal provides flexibility in using an appropriate quantity of the Reference Standard to obtain the desired concentration of the *Standard preparation.*

(PA7b: B. Davani) RTS—42674-1

Change to read:

Assay—[NOTE—All solutions must be prepared immediately prior to use and remain refrigerated until use.]

0.01 M Ammonium acetate—Dissolve 0.77 g of ammonium acetate in about 900 mL of water in a 1000-mL volumetric flask. Dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate* and acetonitrile (95 : 5).

Resolution solution—Dissolve accurately weighed quantities of thymine and thymidine in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of 0.1 µg of each component per mL.

Standard preparation— ~~Transfer about 50 mg of USP Stavudine RS, accurately weighed, to a 500-mL volumetric flask, and dissolve in about 200 mL of water, sonicate, dilute with water to volume, and mix.~~

■Using sonication, dissolve an accurately weighed quantity of USP Stavudine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of about 0.1 mg per mL.■2S *(USP29)*

Assay preparation—Open not fewer than 3 Capsules, and dissolve the contents quantitatively in water. Dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.1 mg of stavudine per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 268-nm detector and a 4.6-mm × 3.3-cm column that contains packing L1. The flow rate is about 0.7 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between thymine and thymidine is not less than 2.0, and thymine is resolved from the void volume. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for the stavudine peak is between 2.8 and 5.0 minutes; the column efficiency is not less than 800 theoretical plates; the tailing factor is not more than 1.8; 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 stavudine ($C_{10}H_{12}N_2O_4$) in each Capsule taken by the formula:

$$C(V/N)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Stavudine RS in the *Standard preparation; V* is the volume, in mL, used to prepare the *Assay preparation; N* is the number of Capsules 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.

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BRIEFING

Succinylcholine Chloride, *USP 28* page 1807 and page 74 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to delete the test for *Limit of ammonia salts* because it is an odor test, and there are potential safety concerns. The procedure for *Chromatographic purity, Test 1* is revised to clarify the data obtained from the *System suitability solution* and the *Standard solution.*

(PA1: K. Russo) RTS—42915-1; 42936-1

Delete the following:

■~~**Limit of ammonium salts**—To about 200 mg add 5 mL of sodium carbonate TS, and bring to a boil: no odor of ammonia is evolved.~~■2S (*USP29*)

Change to read:

Chromatographic purity—

TEST 1—

Buffer solution—Prepare a solution in water containing 3.85 g per L of 1-pentanesulfonic acid, 2.9 g per L 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%.~~

■the resolution, *R,* between citric acid and succinic acid is not less than 2.9. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3.0%.■2S (*USP29*)

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, if present (retention time is about 3.5 minutes).

■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.■2S (*USP29*)

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 Succinylmonocholine 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 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~~ ▲0.01▲*USP29* 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 suitable device for chemical suppression, 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 uses a suitable regenerant flow rate 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

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Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between sodium and choline 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 the *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:*~~

▲and▲*USP29*
not more than 1.5% of total impurities is found, the results for *Test 1* and *Test 2* being added.

BRIEFING

Technetium Tc 99m Fanolesomab Injection, page 448 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to revise the *Packaging and storage* section in accordance with the current policies of the Packaging, Storage and Distribution Expert Committee.

(PA5: A.Wilk) RTS—42996-1

Add the following:

▲Technetium Tc 99m Fanolesomab Injection

» Technetium ^{99m}Tc Fanolesomab Injection is a sterile, nonpyrogenic preparation of anti-CD15 antibody, a partially reduced murine IgM monoclonal antibody that is labeled with ^{99m}Tc and is suitable for intravenous administration. It may contain reducing agents, buffers, and stabilizers. It contains no antimicrobial agents. Other chemical forms of radioactivity do not exceed 10 percent of the total radioactivity. *[Caution—Components of the commercial kit that are used to prepare the Injection are not to be administered directly to the patient.]*

Change to read:

Packaging and storage—Preserve in single-dose containers. ■Store in the refrigerator. [NOTE—After radiolabeling, the Technetium Tc 99m Fanolesomab Injection can be kept at room temperature.]■2S *(USP29)*

Labeling—Label it to include the following, in addition to the information specified for *Labeling* under *Injections* ⟨1⟩: the time and date of calibration; the amount of ^{99m}Tc as labeled fanolesomab expressed in MBq (or mCi) per mL at the time of calibration; the expiration date and time; the storage temperature; and the statement "Caution—Radioactive Material". The labeling indicates that the radioactive half-life of ^{99m}Tc is 6.0 hours and that, in making dosage calculations, correction is to be made for radioactive decay. The labeling also states that the Injection is to be used within 6 hours following constitution.

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

Bacterial endotoxins ⟨85⟩**:** not more than 0.1 Endotoxin Unit per µg of fanolesomeb in the prepared Injection.

pH ⟨791⟩**:** between 5.8 and 6.6.

Particulate matter ⟨788⟩—It meets the requirements for particulate matter specified for small-volume injections.

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Radiochemical purity—

SYSTEM 1: *(free pertechnetate ^{99m}Tc)*

Adsorbent: instant thin-layer chromatography (ITLC) strips[1], heat-treated at 110° for 30 minutes.

Test solution—Use the Injection.

Application volume—Apply 3 µL of the *Test solution* to the origin.

Developing solvent system: methyl ethyl ketone (MEK).

Procedure—Apply the *Test solution* about 2 cm from the bottom of the *Adsorbent* strip. Immediately develop by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm from the origin. The radiochemical impurity, free pertechnetate ^{99m}Tc, migrates to the top section, while colloidal ^{99m}Tc and technetium ^{99m}Tc fanolesomab remain near the origin on the bottom section. Allow the chromatogram to air-dry. Determine the distribution of radioactivity on the chromatogram by cutting the developed strip at 4 cm from the bottom and then separately measuring and recording the net radioactivity in the top and bottom sections using a suitable radiation detector. Calculate the percentage of free pertechnetate ^{99m}Tc in the Injection by the formula:

$$100\,A_T/(A_T + A_B),$$

in which A_T is the radioactivity measured on the top section; and A_B is the radioactivity measured on the bottom section.

SYSTEM 2: *(colloidal ^{99m}Tc)*

Adsorbent—Use affinity thin-layer chromatography (ATLC) strips[2] that have been soaked in a solution of 50% newborn calf serum (NBCS)[3] in water and allowed to air-dry overnight.

Test solution—Use the Injection.

Developing solvent system: 4% alcohol in 0.3 M sodium chloride.

Application volume—Prespot the point of origin with 3 µL of *Developing solvent system* followed immediately by 3 µL of the *Test solution*.

Procedure—Apply the *Test solution* about 2 cm from the bottom of the *Adsorbent* strip. Immediately develop the strip by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm above the origin. The radiochemical impurity, colloidal ^{99m}Tc, will remain at the origin, while free pertechnetate ^{99m}Tc and technetium ^{99m}Tc fanolesomab migrate close to the solvent front. Remove the strip, and allow to air-dry. Cut the strip 4 cm from the bottom, and separately measure and record the background-corrected radioactivity found in the top and bottom sections, using a suitable radiation detector. Calculate the percentage of colloidal ^{99m}Tc by the formula:

$$100\,A_B/(A_B + A_T)$$

in which A_B is the radioactivity measured in the bottom section; and A_T is the radioactivity measured in the top section. The sum of the result for free pertechnetate ^{99m}Tc in *System 1* and for colloidal ^{99m}Tc measured in *System 2* is not more than 10%.

[1] ITLC strips for free pertechnetate ^{99m}Tc may be obtained from Sunset Scientific Strips LLC (product number 10503), P.O. Box 3895, Albuquerque, NM 87190-3895.

[2] ATLC strips for colloidal ^{99m}Tc may be obtained from Sunset Scientific Strips LLC (product number 10506), P.O. Box 3895, Albuquerque, NM 87190-3895.

[3] NBCS (heat inactivated) may be obtained from GIBCO/Invitrogen Corp. (catalog number 26010-074), 1600 Faraday Avenue, P.O. Box 6482, Carlsbad, CA 92008.

Immunoreactivity—

Adsorbent—Use affinity thin-layer chromatography (ATLC) strips[2] that have been soaked in a solution of 50% newborn calf serum (NBCS)[3] in water and allowed to air-dry overnight.

Diluent—Prepare a mixture of NBCS and pH 7.4 phosphate-buffered saline (PBS) (1 : 1).

Test solution—Use the Injection diluted with *Diluent* (1 in 4).

REFERENCE MATERIALS—

Positive control: CD15 positive HL-60 (ATCC No. CCL240) formalin fixed-cell suspension (12×10^6 cells per mL).

Negative control: CD15 negative Raji (ATCC No. CCL86) formalin fixed-cell suspension (12×10^6 cells per mL).

Application volume—Thaw, and mix the HL-60 and Raji cell stock suspensions. Dispense 90-µL aliquots into individual incubation tubes. Add 3 µL of the *Test solution* to each incubation tube, and mix on a vortex mixer for 5 seconds. Incubate for 30 minutes with gentle rocking at $37 \pm 2^\circ$.

Developing solvent system—Prepare a solution containing 0.05% sodium azide and 4% alcohol in 10 mM phosphate-buffered saline, pH 7.4 (PBS). Pass through a filter having a porosity of 0.22 µm.

Procedure—Mix each incubation tube on a vortex mixer. Immediately remove, and apply 10 µL of sample to the origin of the *Adsorbent* ATLC strip (2 cm from bottom). Allow the sample to adsorb onto the strip, and immediately develop the strip by ascending chromatography (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩) until the solvent front has moved about 7.5 cm from the origin. Remove the strips, and allow to air-dry. Cut both strips 4 cm above the origin. Separately measure and record the background-corrected radioactivity found on the top and bottom sections of each strip, using a suitable radiation detector. Immunoreactive technetium ^{99m}Tc fanolesomab, bound to the HL-60 cells, remains at the origin, while nonbound forms of ^{99m}Tc migrate away from the origin. Nonspecific binding is measured using the Raji negative control cells. Calculate the specific immunoreactive binding by the formula:

$$[100A_{B(HL\text{-}60)}/(A_{B(HL\text{-}60)} + A_{T(HL\text{-}60)})] - [100A_{B(Raji)}/(A_{B(Raji)} + A_{T(Raji)})]$$

in which $A_{B(HL\text{-}60)}$ and $A_{B(Raji)}$ are the radioactivity of the HL-60 positive control cells and Raji negative control cells, respectively, measured on the bottom section of each strip; and $A_{T(HL\text{-}60)}$ and $A_{T(Raji)}$ are the radioactivity of the HL-60 positive control cells and Raji negative control cells measured on the top section of each strip. A minimum specific immunoreactive binding of 40% is required for the CD15-positive HL-60 cells.

Other requirements—It meets the requirements for *Radionuclide identification* and *Radionuclidic purity* under *Sodium Pertechnetate Tc 99m Injection*. It also meets the requirements under *Injections* ⟨1⟩, except that it may be distributed or dispensed prior to completion of the test for *Sterility,* the latter test being started on the date of manufacture.

Assay for radioactivity ⟨821⟩**—**Using a suitable counting assembly (see *Selection of a Counting Assembly*), determine the radioactivity, in MBq (or mCi) per mL, of Injection by use of a calibrated system.▲*USP29*

In-Process Revision

BRIEFING

Triclosan, *USP 28* page 1971 and page 2054 of *PF* 30(6) [Nov.–Dec. 2004]. It is proposed to revise the *Standard preparation* and the *Assay preparation* in the *Assay* to replace dichloromethane, a potential occupational carcinogen, with ethyl acetate. It is also proposed in the *Assay* to further dilute the *Standard preparation* and the *Assay preparation* and to increase the injected volume in the *Procedure* to minimize column deterioration.

(PA7b: B. Davani) RTS—42199-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP 2,4-Dichlorophenol RS. USP Parachlorophenol RS.*▲*USP29*
USP Triclosan RS.

▲*USP Triclosan Related Compounds Mixture A RS.*▲*USP29*

Change to read:

Limit of monochlorophenols and 2,4-dichlorophenol—

Phosphate buffer—Transfer about 1.38 g of anhydrous monobasic sodium phosphate and about 1.42 g of dibasic sodium phosphate to a 1-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Phosphate buffer* (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Quantitatively dissolve accurately weighed quantities of ~~4-chlorophenol and 2,4-dichlorophenol~~

▲USP Parachlorophenol RS and USP 2,4-Dichlorophenol RS▲*USP29*
in acetonitrile, dilute with an equal volume of water, and mix. Transfer a portion of this solution to a suitable container, and dilute quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water (1 : 1) to obtain a solution having known concentrations of about 0.5 µg of ~~4-chlorophenol~~

▲parachlorophenol▲*USP29*
and 0.1 µg of 2,4-dichlorophenol per mL.

Test solution—Transfer about 250 mg of Triclosan, accurately weighed, to a 25-mL low-actinic volumetric flask, dissolve in 20 mL of acetonitrile, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a coulometric electrochemical detector with electrode 1 set at 0.45 V and electrode 2 set at 0.75 V, both having a positive (oxidative) polarity, and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 9.0% for 2,4-dichlorophenol.

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. The peak responses for ~~4-chlorophenol~~

▲parachlorophenol▲*USP29*
and 2,4-dichlorophenol in the chromatogram of the *Test solution* are not greater than the corresponding peaks in the chromatogram of the *Standard solution*.

Change to read:

Limit of 1,3,7-trichlorodibenzo-*p*-dioxin, 2,8-dichlorodibenzo-*p*-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and glacial acetic acid (70 : 30 : 0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Standard solution*—Transfer accurately weighed quantities of 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran to a volumetric flask, add accurately measured volumes of 1,3,7-trichlorodibenzo-*p*-dioxin and 2,8-dichlorodibenzo-*p*-dioxin, and dissolve in methanol. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having concentrations of about 0.5, 1.0, 0.5, and 1.0 µg per mL, respectively.~~

▲▲*USP29*
Test solution—Transfer about 2.0 g of Triclosan, accurately weighed, to a screw-capped centrifuge tube, add 5 mL of 2 N potassium hydroxide, and shake for 10 minutes to dissolve. Add 3 mL of *n*-hexane, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, add another 3 mL of *n*-hexane to the aqueous layer, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to the previous extract, discard the aqueous layer, add 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 minutes, and allow the phases to separate. Discard the aqueous layer, add another 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, and evaporate with the aid of a stream of nitrogen to dryness. Dissolve the residue in 1.0 mL of methanol, 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 packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the ~~*Standard solution,*~~

▲USP Triclosan Related Compounds Mixture A RS,▲*USP29*
and record the peak responses as directed for *Procedure:* the relative retention times are about 0.59 for 2,8-dichlorodibenzofuran, 0.71 for 2,8-dichlorodibenzo-*p*-dioxin, 0.88 for 2,4,8-trichlorodibenzofuran, and 1.0 for 1,3,7-trichlorodibenzo-*p*-dioxin; and the relative standard deviation for replicate injections is not more than 15.0%, determined from the 2,8-dichlorodibenzo-*p*-dioxin peak.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. ~~The peak responses for 2,8-dichlorodibenzofuran, 2,8-dichlorodibenzo-*p*-doxin, 2,4,8-trichlorodibenzofuran, and 1,3,7-trichlorodibenzo-*p*-dioxin obtained from the *Test solution* are not greater than the corresponding peaks obtained from the *Standard solution*~~

In-Process Revision

▲Calculate the concentration of each analyte in the portion of Triclosan taken by the formula:

$$(C/W)(r_i/r_S)$$

in which C is the concentration, in µg per mL, of the respective analyte in the USP Triclosan Related Compounds Mixture A RS; W is the weight, in g, of Triclosan taken; and r_i and r_S are the peak responses for the respective analyte obtained from the *Test solution* and the USP Triclosan Related Compounds Mixture A RS, respectively: not more than 0.25 ppm of 2,8-dichlorodibenzofuran is found; not more than 0.5 ppm of 2,4,8-trichlorodibenzofuran is found; not more than 0.25 ppm of 1,3,7-trichlorodibenzo-*p*-dioxin is found; and not more than 0.5 ppm of 2,8-dichlorodibenzo-*p*-dioxin is found.▲*USP29*

Change to read:

Assay—
Standard preparation—Dissolve an accurately weighed quantity of USP Triclosan RS in ~~dichloromethane~~

■ethyl acetate,■2S (*USP29*)
and dilute quantitatively, and stepwise if necessary, with ~~dichloromethane~~

■ethyl acetate■2S (*USP29*)
to obtain a solution having a known concentration of about 4.0 mg per mL.
Assay preparation—Transfer about 40 mg of Triclosan, accurately weighed, to a ~~10-mL~~

■100-mL■2S (*USP29*)
volumetric flask, dissolve in and dilute with ~~dichloromethane~~

■ethyl acetate■2S (*USP29*)
to volume, and mix.
Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 15-m capillary column with phase G3. The carrier gas is helium maintained at about 6 psi. The injection port temperature is maintained at 34° and is increased rapidly to 200° immediately after the injection, the column temperature is maintained at 34°, and the detector temperature is maintained at 260°. 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 ~~0.5~~

■2.0■2S (*USP29*)
µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, increase the column temperature by 20° per minute to 140°, then increase column temperature by 4° per minute to 240°, maintain this temperature for not less than 5 minutes, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{12}H_7Cl_3O_2$ in the portion of Triclosan taken by the formula:

~~$10C(r_U/r_S)$~~

■$100C(r_U/r_S)$■2S (*USP29*)

in which C is the concentration, in mg per mL, of USP Triclosan 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

Trimethoprim, *USP 28* page 1987. On the basis of new stability data received, it is proposed to change the storage condition in *Packaging and storage* to room temperature.

(PA7b: B. Davani) RTS—42999-1

Change to read:

Packaging and storage—Preserve in tight, light-resistant containers. ~~Store at 25°, excursions permitted between 15° and 30°.~~

■Store at room temperature.■2S (*USP29*)

In-Process Revision

BRIEFING

Tryptophan, *USP 28* page 1999. It is proposed to revise the tests for *Chloride* and for *Sulfate* to add a *Note* indicating that heating of the sample preparation may be necessary to assist in dissolution of the sample.

(DSN: L. Evans) RTS—42190-2

Change to read:

Chloride ⟨221⟩—A 0.73-g portion shows no more chloride than corresponds to 0.50 mL of 0.020 N hydrochloric acid (0.05%).

■[NOTE—Gently heat the sample preparation to dissolve, if necessary.]■2S (*USP29*)

Change to read:

Sulfate ⟨221⟩—A 0.33-g portion shows no more sulfate than corresponds to 0.10 mL of 0.020 N sulfuric acid (0.03%).

■[NOTE—Gently heat the sample preparation to dissolve, if necessary.]■2S (*USP29*)

BRIEFING

Tylosin Tartrate. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The *Content of tylosins* test is an HPLC method utilizing a 4.6-mm × 20-cm column that contains 5-µm packing L1. USP has received validation data indicating that a Zorbax SB C18 column is suitable for this method. Interested parties are encouraged to submit comments.

(VET: I. DeVeau) RTS—41977-1

In-Process Revision

Add the following:

■Tylosin Tartrate

(10*E*,12*E*)-(3*R*,4*S*,5*S*,6*R*,8*R*,14*S*,15*R*)-14-[(6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyl)oxymethyl]-5-[[3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-ribo-hexopyranosyl)-3-dimethylamino-β-D-glucopyranosyl]oxy]-6-formylmethyl-3-hydroxy-4,8,12-trimethyl-9-oxoheptadeca-10,12-dien-15-olide.

Tylosin A (Tylosin) 916.10 [*1401-69-0*].

» Tylosin Tartrate is a tartrate of a mixture of macrolide antibiotic substances, or the mixture of such substances, produced by the growth of *Streptomyces fradiae,* or by any other means. Its potency is not less than 800 µg of tylosin per mg, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, protected from light, moisture, and excessive heat. Store at 25°, excursions permitted between 15° and 30°.

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

USP Reference standards ⟨11⟩—*USP Tylosin RS*. *USP Tylosin Tartrate RS*.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak for tylosin A 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 tylosins*.

C: It responds to the test for *Tartrate* ⟨191⟩.

pH ⟨791⟩**:** between 5.0 and 7.2 in a solution prepared by dissolving 0.25 g in 10 mL of carbon dioxide-free water.

Loss on drying ⟨731⟩—Dry about 1 g, accurately weighed, in vacuum at a pressure of not more than 5 mm of mercury at 60° for 3 hours: it loses not more than 4.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 2.5%, the charred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

Limit of tyramine—In a 25.0 mL volumetric flask, dissolve 50.0 mg of tylosin in 5.0 mL of a 3.4 g per L solution of phosphoric acid. Add 1.0 mL of pyridine and 2.0 mL of a saturated solution of ninhydrin (about 40 g per L). Close the flask with aluminum foil, and heat in a water bath at 85° for 30 minutes. Cool the solution rapidly to room temperature, and dilute with water to volume. Mix, and measure immediately the absorbance (see *Spectrophotometry and Light-Scattering* ⟨851⟩) of the solution at 570 nm against a blank solution prepared in a similar manner. The absorbance is not greater than that of a standard prepared at the same time and in the same manner using 5.0 mL of a 35 mg per L solution of tyramine in a 3.4 g per L solution of phosphoric acid. If intended for use in the manufacture of parenteral dosage forms, the absorbance is not greater than that of a standard prepared at the same time and in the same manner using 5.0 mL of a 15 mg per L solution of tyramine in a 3.4 g per L solution of phosphoric acid.

Content of tylosins—

Mobile phase—Prepare a mixture of filtered 200 g per L of sodium perchlorate, previously adjusted with 1 N hydrochloric acid to a pH of 2.5 ± 0.1, and acetonitrile (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Tylosin RS in a mixture of acetonitrile and water (1 : 1) to obtain a solution having a known concentration of about 0.2 mg per mL. [NOTE—Prepare the *Standard solution* immediately before use.]

Test solution—Dissolve an accurately weighed quantity of Tylosin in a mixture of acetonitrile and water (1 : 1) to obtain a solution having a known concentration of about 0.2 mg per mL. [NOTE—Prepare the *Test solution* immediately before use.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 290-nm detector and a 4.6-mm × 20-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute and the column temperature is maintained at 35°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the order of elution is tylosin C, tylosin B, tylosin D, and tylosin A with relative retention times of about 0.5, 0.6, 0.8, and 1.0 minutes, respectively; the resolution of the peaks representing tylosin D and tylosin A is not less than 2.0; the tailing factors are not more than 1.5; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms over a period of time equivalent to 1.5 times the elution time of the main tylosin A peak, and measure the peak areas for all the peaks. Calculate the percentages of tylosin A, tylosin B, tylosin C, and tylosin D in the Tylosin taken by the formula:

$$100(r_I / r_S)$$

in which r_I is the area of the tylosin A peak, the tylosin B peak, tylosin C peak, or the tylosin D peak, as appropriate, in the chromatogram obtained from the *Test solution;* and r_S

is the sum of the areas of all of the peaks in the chromatogram obtained from the *Test solution:* the content of tylosin A is not less than 80%; and the sum of the contents of tylosin A, tylosin B, tylosin C, and tylosin D is not less than 95%.

Assay—Proceed as directed for Tylosin under *Antibiotics—Microbial Assays* ⟨81⟩. Prepare the *Test Dilution* as follows. Transfer an accurately weighed quantity of Tylosin Tartrate, equivalent to about 250 mg of tylosin, to a 500-mL volumetric flask, add 50 mL of methanol, and swirl to dissolve. Dilute with *Buffer No. 3* to volume, and mix. Transfer 4.0 mL of this solution to a second 500-mL volumetric flask, dilute with a mixture of *Buffer No. 3* and methanol (1 : 1), and mix. This solution contains about 4 µg of tylosin per mL.■2S (*USP29*)

BRIEFING

Valproic Acid Injection, page 801 of *PF* 31(3) [May–June 2005]. *Valproic Acid Injection,* the title of the proposed monograph for this dosage form, is proposed to be included in the *First Supplement* to *USP 29–NF 24* along with the monograph. However, it is proposed that the title have an official date of October 1, 2007, which is 18 months later than the official date of the *First Supplement,* April 1, 2006. The use of this title would be permitted as of April 1, 2006, but it would not become mandatory until October 1, 2007. The 18-month extension is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the terminology.

(NL: L. Paul) RTS—22708-2

In-Process Revision

Add the following:

■Valproic Acid Injection

•***(Title for this new monograph—to become official October 1, 2007)***•2

» Valproic Acid Injection is a sterile aqueous solution of sodium valproate, formed from the interaction of Valproic Acid and Sodium Hydroxide, in Water for Injection, and one or more suitable buffering or sequestering agents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of valproic acid ($C_8H_{16}O_2$). Valproic Acid Injection contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose *Containers for Injection* as described under *Injections* ⟨1⟩, preferably of Type I glass. Store at controlled room temperature, excursions allowed between 15° and 30°.

Labeling—Label it to state the name and quantity of any buffering or sequestering agent used.

USP Reference standards ⟨11⟩**—***USP Endotoxin RS. USP Valproic Acid RS.*

Identification—

A: 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.*

B: It meets the requirements of the tests for *Sodium* ⟨191⟩.

Bacterial endotoxins ⟨85⟩—It contains not more than 23 USP Endotoxin Units per mL of Injection.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* in *Test for Sterility of the Product To Be Examined.*

pH ⟨791⟩**:** between 7.0 and 9.0.

Particulate matter ⟨788⟩—It meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Internal standard solution—Dissolve a quantity of biphenyl in methylene chloride to obtain a solution containing 5 mg per mL.

Standard stock preparation—Prepare a solution of USP Valproic Acid RS in *Internal standard solution* having a concentration of about 8 mg per mL.

Standard preparation—Transfer 5.0 mL of *Standard stock preparation* into a 50-mL volumetric flask, and dilute with methylene chloride to volume.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to 400 mg of valproic acid, into a suitable container; add about 20 mL of 5% (v/v) hydrochloric acid; shake by mechanical means for 2 minutes; add 50.0 mL of *Internal standard solution;* and shake by mechanical means for 1 hour. Allow the phase to separate (approximately 1 hour). The bottom organic layer remains cloudy, and at times a slight emulsion may persist. The emulsion is easily broken up with the aid of a glass rod. Pipet 5 mL of the extract from the bottom organic layer into a 50-mL volumetric flask, and dilute with methylene chloride.

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 G34 on 80- to 100-mesh support S1A. The column temperature is maintained at about 155°, the injection port temperature is maintained at about 275°, and the detector block temperature is maintained at about 300°. Dry helium is used as the carrier gas, at a flow rate of about 20 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the resolution, *R,* between the valproic acid and biphenyl peaks is not less than 3.0; and the relative standard deviation of the peak area ratios for replicate injections is not more than 2.0%.

Procedure—Separately inject equal amounts (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for the valproic acid and biphenyl peaks. Calculate the quantity, in mg, of valproic acid in the portion of Injection taken by the formula:

$$C(R_U / R_S) D$$

in which C is the concentration, in mg per mL, of USP Valproic Acid RS in the *Standard preparation;* R_U and R_S are the peak area ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively; and D is the appropriate dilution factor used to prepare the *Assay preparation.*■1S (*USP29*)

In-Process Revision

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 23* page 2941, page 3647 of the *Second Supplement,* and page 1128 of *PF* 31(4) [July–Aug. 2005]. It is proposed to add *Erythritol* to the *Humectant* and *Sweetening Agent* categories to complement the proposed new monograph *Erythritol,* which appears elsewhere in this issue of *PF.*

(EMC) RTS—42741-1

Change to read:

Coating Agent

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
▲Cellaburate▲*NF23*
Cellulose Acetate Phthalate (see Cellacefate)
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■1S (*NF24*)

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
■Hypromellose Acetate Succinate■2S (*NF23*)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
■Maltodextrin■2S (*NF23*)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
■Starch, Pregelatinized Modified■1S (*NF23*)
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Humectant

■Corn Syrup Solids■1S (*NF24*)

■Erythritol■2S (*NF24*)
Glycerin
Hexylene Glycol

■Maltitol■2S (*NF24*)
Propylene Glycol
Sorbitol
■Sorbitol Sorbitan Solution■2S (*NF23*)

■Tagatose■1S (*NF24*)

Change to read:

Ointment Base
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Diethylene Glycol Monoethyl Ether

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Lanolin
Ointment, Hydrophilic
Ointment, White
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Ointment, Yellow
Polyethylene Glycol ■Monomethyl Ether■2S (*NF23*)
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water
Squalane
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Vegetable Oil, Hydrogenated, Type II

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
▲Cellaburate▲*NF23*
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■1S (*NF24*)
▲Sodium Tartrate▲*NF23*

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Change to read:

Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Peanut Oil
Polyethylene Glycol
■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol
Sesame Oil
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent

Acacia
Agar
■Alamic Acid■2S (*NF23*)
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 Copolymer

▲Carbomer Homopolymer▲*NF24*
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■1S (*NF24*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
■Maltodextrin■2S (*NF23*)
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent

▲Acesulfame Potassium▲*NF23*
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■1S (*NF24*)
Dextrates
Dextrose
Dextrose Excipient

■Erythritol■2S (*NF24*)
Fructose
▲Galactose▲*NF23*

■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder

Acacia
Alginic Acid

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)

Ammonio Methacrylate Copolymer Dispersion

▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■1S (*NF24*)
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
■Hypromellose Acetate Succinate■2S (*NF23*)
■Maltodextrin■2S (*NF23*)
Maltose
Methylcellulose
Polyethylene Oxide
Povidone
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Syrup

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■1S (*NF24*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose Monohydrate

■Maltitol■2S (*NF24*)
■Maltodextrin■2S (*NF23*)
Maltose
Mannitol
Sorbitol
■Starch■2S (*NF23*)
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

■Corn Syrup Solids■1S (*NF24*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■1S (*NF24*)
■Dextrose■2S (*NF23*)
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

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MONOGRAPHS (NF)

BRIEFING

Calcium Silicate, *NF 23* page 2970 and page 595 of *PF* 30(2) [Mar.–Apr. 2004]. On the basis of comments received, it is proposed to replace the current test for *Limit of lead* with a revised version using a graphite furnace atomic absorption method with Zeeman background correction. Additional changes have been added in the revised test proposal for *Limit of fluoride.* It is also proposed to add a new *USP Reference standards* section to include USP Sodium Fluoride RS.

(EMC: C. Sheehan) RTS—41797-1; 41797-2; 41593-1

Change to read:

» Calcium Silicate,

▲crystalline or amorphous,▲*NF24*
is a compound of calcium oxide and silicon dioxide. It contains not less than 4.0 percent of calcium oxide and not less than ~~45.0~~

▲35.0▲*NF24*
percent of silicon dioxide.

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Sodium Fluoride RS.*■2S (*NF24*)

Change to read:

pH ⟨791⟩**:** between 8.4 and ~~10.2,~~

▲11.2,▲*NF24*
determined in a well-mixed aqueous suspension (1 in 20).

Delete the following:

■~~**Lead** ⟨251⟩—Dissolve 1.0 g in 20 mL of 3 N hydrochloric acid, evaporate on a steam bath to about 10 mL, dilute with water to about 20 mL, and cool: the limit is 0.001%.~~■2S (*NF24*)

Add the following:

■**Limit of lead—**

Nitric acid diluent—Transfer 42 mL of nitric acid, 65 percent to a 1000-mL volumetric flask. Dilute with water to volume, and mix.

Test solution—Accurately weigh 2.0 g of Calcium Silicate into a 150-mL beaker. Mix with 50 mL of *Nitric acid diluent.* Cover with a watch glass, and boil for 20 minutes. Allow to cool. With the aid of a vacuum, pass through a glass filter[1] and wash the filter several times with water. Transfer the filtrate into a 100-mL volumetric flask. Dilute with water to volume, and mix.

Matrix modifier solution—Transfer 1.0 mL of palladium matrix modifier and 100 uL of magnesium matrix modifier to a 20-mL volumetric flask. Dilute with water to volume, and mix.

Standard lead solution—Transfer 100 uL of lead standard solution to a 100-mL volumetric flask. Dilute with water to volume, and mix. This solution contains the equivalent of 1.0 µg of lead per mL.

Calibration solutions—To a series of 100-mL volumetric flasks, pipette 0, 1, and 5 mL of the *Standard lead solution*, and dilute with 50 mL of *Nitric acid diluent*. Dilute with water to volume, and mix. These solutions contain 0, 0.01, and 0.05 µg of lead per mL, respectively.

System suitability solution—Transfer 5 mL of *Standard lead solution* and 50 mL of *Nitric acid diluent* into a 100-mL volumetric flask. Dilute with water to volume, and mix. This solution contains the equivalent of 0.05 µg of lead per mL.

Procedure—Concomitantly determine the absorbances of the *Calibration solutions, Test solution,* and *System suitability solution* at the lead emission line at 283.3 nm with a suitable graphite furnace atomic absorption spectrophotometer equipped with a lead hollow-cathode lamp using argon as the carrier gas and an adequate means of Zeeman background correction. Under typical conditions, the *Test solution* and *Calibration solutions* volumes are 20 µL, the

[1] Glass filter: Whatman GF/B glass microfiber filters, 1.0 µm, Watman no. 1821-090. Available as catalog number 28497-492, from VWR, www.vwr.com.

volume of the *Matrix modifier solution* is 10 µL, the injection temperature is 20°, and the oven conditions are as follows (see *Table 1*). [NOTE—These conditions may be optimized for each instrument.]

Table 1.

Step	Temperature
Drying 1	110°
Drying 2	130°
Pyrrolysis	950°
Read	1800°
Clean out	2450°

Run the calibration curve; the correlation coefficient is not less than 0.99; and the recovery for the *System suitability solution* is between 85% and 115%. Calculate the percentage of lead concentration in the *Test solution:* not more than 0.001%, is found.■2S *(NF24)*

Change to read:

Limit of fluoride—

~~NOTE—Store all solutions in plastic containers.~~

~~*Buffer solution*—Add 800 mL of hot water to 74.4 g of edetate disodium and 24.2 g of tris(hydroxymethyl)aminomethane, and stir until dissolved. Adjust with 5 N sodium hydroxide to a pH of 7.5 to 7.6. Allow the solution to cool, and adjust with 5 N sodium hydroxide to a pH of 8.0. Dilute with water to 1000 mL, and mix.~~

~~*Electrode system*—Use a fluoride specific, ion indicating electrode and a calomel reference electrode connected to a pH meter capable of measuring potentials with a reproducibility of ± 0.2 mV (see *pH* ⟨791⟩).~~

~~*Standard stock solution*—Dissolve an accurately weighed quantity of USP Sodium Fluoride RS quantitatively in water to obtain a solution containing 221 µg per mL. Each mL of this stock solution contains 100 µg of fluoride ion.~~

~~*Standard solutions*[NOTE—Prepare on the day of use.] Transfer 10.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains 10 µg of fluoride ion per mL *(Standard solution A).* Transfer 1.0 mL of *Standard stock solution* to a second 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains 1.0 µg of fluoride ion per mL *(Standard solution B).*~~

~~*Test solution*—Transfer 5.0 g of Calcium Silicate to a 150-mL polytef beaker. Add 40 mL of water and 20 mL of 1 N hydrochloric acid. Heat to near boiling for 1 minute, stirring continuously. Cool in an ice bath, transfer the suspension to a 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Transfer 20.0 mL of *Standard solution A, Standard solution B,* and the *Test solution* to separate polytef beakers, add 10.0 mL of *Buffer solution* to each beaker, and stir with a plastic-coated stirring bar. Concomitantly measure the potentials, in mV, of the solutions. [NOTE—When taking measurements, immerse the electrodes in the solution, stir on a magnetic stirrer having an insulated top until equilibrium is attained (1 to 2 minutes), and record the potential. Rinse and dry the electrodes between measurements, taking care to avoid damaging the crystal of the ion-specific electrode.] Plot the logarithms of the fluoride ion concentrations, in µg per mL, of the *Standard solutions* versus potential, in mV. From the measured potential of the *Test solution* and the standard response line, determine the concentration, *C,* in µg per mL, of fluoride ion in the *Test solution.* Calculate the quantity, in µg of fluoride per g of Calcium Silicate by multiplying *C* by 20. The limit is 10 µg per g.~~

■NOTE—Store all solutions in plastic containers.

Buffer solution—Transfer 147 g of sodium citrate to a 500-mL volumetric flask, dissolve in and dilute with water to volume.

Ionic strength adjustment buffer—Transfer 42 mL of hydrochloric acid, 121 g of tris(hydroxymethyl)aminomethane, and 115 g of sodium tartrate to a 500-mL volumetric flask containing 250 mL of water. Stir to dissolve, and dilute with water to volume.

Electrode system—Use a fluoride-specific, ion-indicating electrode and a ~~calomel~~ suitable reference electrode connected to a pH meter capable of measuring potentials with a reproducibility of ± 0.2 mV (see *pH* ⟨791⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Sodium Fluoride RS in water to obtain a solution containing 221 µg per mL. Each mL of this stock solution contains 100 µg of fluoride ion.

Test solution—Transfer about 2.0 g of Calcium Silicate, accurately weighed, to a 100-mL ~~plastic~~ polytef beaker containing a magnetic stir bar. Add 20 mL of water and 2.0 mL of hydrochloric acid. Cover with a watch glass, and heat ~~with stirring~~ to a vigorous boil for 1 minute, stirring continuously. Remove from heat, and cool. Transfer the cooled suspension to a 100-mL ~~plastic~~ polytef beaker. Add 25 mL of *Buffer solution,* and adjust with ammonium hydroxide or hydrochloric acid to a pH between 5 and 6. Add 50 mL of *Ionic strength adjustment buffer* and water to make 100 mL of solution.

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Standard response line—Obtain a standard response line with four standard solutions containing 0, 0.10, 0.20, and 0.40 µg per mL of fluoride as follows. Add 23 mL of water, 2 mL of hydrochloric acid, and 25 mL of *Buffer solution* to a 100-mL plastic beaker. Adjust with ammonium hydroxide to a pH between 5 and 6, and add *Ionic strength adjustment buffer* to obtain 100 mL of solution. Insert the electrode into the solution, stir for at least 15 minutes, and record the potential for the *Standard solution* containing 0 µg of fluoride per mL. When the electrode has stabilized, add 100 µL of the *Standard stock solution* to the beaker, and stir. Allow the electrode to stabilize for 5 minutes, and measure the potential for the *Standard solution* containing 0.10 µg of fluoride per mL. Similarly add another 100 µL and 200 µL of the *Standard stock solution* and record the potential for the *Standard solutions,* containing 0.20 µg per mL of fluoride and 0.40 µg per mL of fluoride, respectively. After each addition, continue to stir for 5 minutes before recording the reading.

Procedure—Insert the calibrated electrode into the *Test solution,* stir for 5 minutes, and record the measurement. From the measured potential of the *Test solution* and the standard response line, determine the concentration, *C,* in µg per mL, of fluoride ion in the *Test solution.* Calculate the quantity, in µg per g of fluoride in Calcium Silicate by the formula:

$$100C/W$$

in which *W* is the weight, in g, of Calcium Silicate taken. The limit is 10 µg per g.■2S *(NF24)*

Change to read:

Assay for silicon dioxide—Transfer ~~about 400 mg of Calcium Silicate,~~

▲the appropriate amount of Calcium Silicate (see *Table 2.*)▲*NF24*

accurately weighed, to a beaker, add 5 mL of water and 10 mL of perchloric acid, and heat until dense white fumes of perchloric acid are evolved. Cover the beaker with a watch glass, and continue to heat for ~~15 minutes longer.~~

▲2 hours.▲*NF24*
Allow to cool, add 30 mL of water, filter, and wash the precipitate with 200 mL of hot water. [NOTE—Retain the combined filtrate and washings for use in the *Assay for calcium oxide.*] Transfer the filter paper and its contents to a platinum crucible, heat slowly to dryness, then heat sufficiently to char the filter paper, ~~. After cooling, add a few drops of sulfuric acid, and ignite at about 1300°~~

▲and ignite at about 900° to 1000°▲*NF24*
to constant weight. Moisten the residue with 5 drops of ~~sulfuric~~

▲perchloric▲*NF24*
acid, add 15 mL of hydrofluoric acid, heat cautiously on a hot plate until all of the acid is driven off, and ignite at a temperature not lower than 1000° to constant weight. Cool in a desiccator, and weigh: the loss in weight represents the weight of SiO_2. The percentage of silicon dioxide in the Calcium Silicate is between 90.0% and 110.0% of the content stated in the labeling, or within the range of percentages stated in the labeling.

▲**Table 2.**

Sample Weight	Calcium Oxide Content
about 400 mg	greater than 25%
about 600 mg	11–25%
about 1000 mg	4–10%

▲*NF24*

Change to read:

Assay for calcium oxide—Neutralize the combined filtrate and washings retained from the *Assay for silicon dioxide* to litmus with 1 N sodium hydroxide. Add, while stirring, about ~~30 mL~~

▲10 mL▲*NF24*
of 0.05 M edetate disodium VS from a 50-mL buret. Add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Each mL of 0.05 M edetate disodium is equivalent to 2.804 mg of CaO. The percentage of CaO in the Calcium Silicate is between 90.0% and 110.0% of the content stated in the labeling, or within the range of percentages stated in the labeling.

Change to read:

Ratio of silicon dioxide to calcium oxide—Divide the percentage of silicon dioxide obtained in the *Assay for silicon dioxide* by the percentage of calcium oxide obtained in the *Assay for calcium oxide:* the quotient obtained is between ~~1.3~~

▲0.5▲*NF24*
and 20.

BRIEFING

Carboxymethylcellulose Calcium, *NF 23* page 2976. It is proposed to revise the sample preparation in the test for *Heavy metals* to align it with recent changes to USP general chapter *Heavy Metals* ⟨231⟩.

(EMC: J. Lane) RTS—42876-1

Change to read:

Heavy metals,

■*Method II*■2S (*NF24*)
⟨231⟩: ~~Determine as directed in the test for *Heavy metals* under *Methylcellulose,* except to use only 1 g of Carboxymethylcellulose Calcium. The limit is 0.002%.~~

■0.002%, adding 1 mL of hydroxylamine hydrochloride solution (1 in 5) to the solution of the residue.■2S (*NF24*)

BRIEFING

Carboxymethylcellulose Sodium 12, *NF 23* page 2978 and page 1139 of *PF* 31(4) [July–Aug. 2005]. It is proposed to revise the sample preparation in the test for *Heavy metals* to align it with recent changes to *USP* general chapter *Heavy Metals* ⟨231⟩.

(EMC: J. Lane) RTS—42876-3

Change to read:

Labeling—Label it to indicate the

■nominal■2S (*NF24*)
viscosity in solutions of stated concentrations of either 1% (w/w) or 2% (w/w).

■The indicated viscosity may be in the form of a range encompassing 80.0% to 120.0% of the nominal viscosity, where the solution concentration is 1% (w/w); and 75.0% to 140.0% of the nominal viscosity, where the solution concentration is 2% (w/w).■2S (*NF24*)

Change to read:

Viscosity ⟨911⟩—Determine the viscosity in a water solution at the concentration stated on the label. Using undried Carboxymethylcellulose Sodium 12, weigh accurately the amount which, on the dried basis, will provide 200 g of solution of the stated concentration. Add the substance in small amounts to about 180 mL of stirred water contained in a tared, wide-mouth bottle, continue stirring rapidly until the powder is well wetted, add sufficient water to make the mixture weigh 200 g, and allow to stand, with occasional stirring, until solution is complete. Adjust the temperature to 25 ± 0.2°, and determine the viscosity, using a rotational type of viscosimeter, making certain that the system reaches equilibrium before taking the final reading. The viscosity of solutions of 2% concentration is not less than 80.0% and not more than 120.0% of that stated on the label; the viscosity of solutions of 1% concentration is not less than 75.0% and not more than 140.0% of that stated on the label

■or it is between the maximum and minimum values, where stated as a range of viscosities.■2S (*NF24*)

Change to read:

~~**Heavy metals—**~~

■**Heavy metals,** *Method II* ⟨231⟩:■2S (*NF24*)
~~Determine as directed in the test for *Heavy metals* under *Methylcellulose,* using a 1.0-g specimen: the limit is 20 µg per g.~~

■0.002%, adding 1 mL of hydroxylamine hydrochloride solution (1 in 5) to the solution of the residue.■2S (*NF24*)

BRIEFING

Cellaburate, *NF 23* page 2981. It is proposed to revise the monograph to include a *Packaging and storage* section.

(EMC: D. Bempong) RTS—42705-1

Cellaburate

(Title for this new monograph—to become official January 1, 2010)

Add the following:

■**Packaging and storage—**Preserve in tight containers. No storage requirements specified.■2S (*NF24*)

In-Process Revision

BRIEFING

Microcrystalline Cellulose, *NF 23* page 2982, page 3353 of the *First Supplement,* and page 1139 of *PF* 31(4) [July–Aug. 2005]. It is proposed to revise *Identification* test *B* to allow for different volumes to be employed to load the viscosimeter, as different capillary-type viscosimeters require different volumes.

(EMC: J. Lane) RTS—42832-1

Change to read:

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, proceed as directed under ~~*Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩;~~

■*Particle size distribution*. The labeling indicates with which technique the particle size distribution was determined if a technique other than analytical sieving was used; and■2S (*NF24*)
the labeling indicates the d_{10}, d_{50}, and d_{90} values ~~(see *Powder Fineness* ⟨811⟩)~~

■■2S (*NF24*)
and the range for each.

Change to read:

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~~

■an appropriate volume■2S (*NF24*)
of the solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscosimeter. Allow the solution to equilibrate at $25 \pm 0.1^\circ$ for not less than 5 minutes. Time the flow between the two 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:

$$t_1(k_1)$$

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, 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.

Change to read:

~~**Particle size distribution estimation by analytical sieving** ⟨786⟩~~

■**Particle size distribution**■2S (*NF24*)
—[NOTE—In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.] Where the labeling states the particle size distribution, determine the particle size distribution as directed in ~~the chapter~~

■*Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩ or by a suitable validated procedure.■2S (*NF24*)

BRIEFING

Powdered Cellulose, page 3353 of the *First Supplement.* It is proposed to revise *Identification* test *B* so that different volumes can be used with a variety of capillary-type viscosimeters that have different volume requirements.

(EMC: J. Lane) RTS—42832-2

Change to read:

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. Im-

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mediately 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~~

■an appropriate volume■2S (*NF24*)
of the solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscosimeter. Allow the solution to equilibrate at 25 ± 0.1° for not less than 5 minutes. Time the flow between the two 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, 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 greater than 440.

BRIEFING

Diethanolamine, *NF 23* page 2998. It is proposed to replace the current *Identification* test with a revised version using a spectrophotometric identification test employing *Infrared Absorption* ⟨197F⟩. It is also proposed to include a new USP Reference Standard, USP Diethanolamine RS, to be used in the *Identification* test.

(EMC: C. Sheehan) RTS—42836-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Diethanolamine RS.*■2S (*NF24*)

Change to read:

Identification, ~~— The IR absorption spectrum, between 6.6 µm and 12.5 µm, of a thin film of it exhibits maxima at about 6.8 µm, 7.3 µm, 8.1 µm, 8.3 µm, 8.9 µm, 9.4 µm, 10.6 µm, and 11.6 µm~~

■*Infrared Absorption* ⟨197F⟩.■2S (*NF24*)

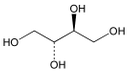
BRIEFING

Erythritol. Because there is no existing monograph for this excipient, a new monograph, based on the monograph appearing in the *European Pharmacopoeia* 5.0, is proposed. The liquid chromatographic procedure in the *Assay* is based on analysis performed with a brand of L17 column or equivalent.The typical retention time for erythritol is about 11 minutes. Interested parties are encouraged to comment on the proposal.

(EMC: C. Sheehan; AMB: R. Tirumalai; NL: L. Paul) RTS—42741-1

Add the following:

■Erythritol



$C_4H_{10}O_4$ 122.12

1,2,3,4-Butanetetrol.

Butane1,2,3,4-tetrol (*meso*-erythritol) [*149-32-6*].

» Erythritol is obtained by fermentation of starch enzyme hydrolysate (from starches such as wheat and corn). It is obtained from the fermentation broth of suitable osmophilic yeasts such as *Moniliella pollinis* or *Trichosporonoides megachilien-*

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sis. It contains not less than 96.0 percent and not more than 102.0 percent of $C_4H_{10}O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

USP Reference standards ⟨11⟩—*USP Erythritol RS.*

Identification—

A: *Infrared Absorption* ⟨191K⟩.

B: *Melting range* ⟨741⟩: between 119° and 123°.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours; it loses not more than 0.2% of its weight. Use about 8 g of sample.

Water, *Method I* ⟨921⟩**:** 0.5%.

Conductivity—Dissolve 20.0 g of Erythritol in a 100-mL volumetric flask, and dilute with the same solvent to volume. Using an appropriate conductivity meter, choose a conductivity cell that is appropriate for the properties and conductivity of the solution to be examined. Use a certified reference material[1] —for example, a solution of potassium chloride—that is appropriate for the measurement. The conductivity value of the certified reference material should be near the expected conductivity value of the solution to be examined. After calibrating the apparatus with a certified reference material solution, rinse the conductivity cell several times with water and at least twice with the aqueous solution to be examined. Measure the conductivity of the solution at a temperature of 20° while stirring gently with a magnetic stirrer: the conductivity is not more than 20 µS per cm.

[1] Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Standards and Technology (NIST), may be used. Solutions prepared according to instructions given in the American Society for Testing and Materials (ASTM) Standard D1125 may be used, provided that the conductivity of the resultant solution is the same as that of the solution prepared from the NIST-certified material.

Microbial limits ⟨61⟩—The total aerobic microbial 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 102 cfu per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Limit of lead—

Standard lead solution—Prepare as directed for *Special Reagents* under *Heavy Metals* ⟨231⟩.

Test solution—Dissolve 20.0 g of Erythritol in diluted acetic acid, and dilute with diluted acetic acid to 100 mL. Add 2.0 mL of a saturated ammonium pyrrolidinedithiocarbamate solution (containing about 10 g of ammonium pyrrolidinedithiocarbamate per L) 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 Erythritol.

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 *Standard lead solution* in addition to the 20.0 g of Erythritol.

Procedure—Set the atomic absorption spectrophotometer to zero, using methyl isobutyl ketone previously treated as described under *Test solution,* but without sample added. Use a lead hollow-cathode lamp as source of radiation, an air–acetylene flame, and an analysis wavelength of 283.3 nm. Introduce the *Test solution* and each of the three *Standard solutions* into the instrument. Record the steady absorbance reading. Plot the absorbance readings against the known concentrations of added lead (in µg), and draw a straight line. Extrapolate the line until it meets the concen-

tration axis, which is equal to the concentration, in mg per kg, of nickel in the sample. Not more than 0.5 mg per kg is found.

Related compounds—

Mobile phase, Assay preparation, Standard preparation, System suitability preparation, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Standard solution—Transfer 2.0 mL of the *Standard preparation* to a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains about 1 mg of erythritol per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Assay preparation* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity found by the formula:

$$VC/W\,(r_i/r_S)$$

in which V is the volume, in mL, of the *Test solution;* C is the concentration, in mg per mL, of Erythritol in the *Standard solution;* W is the amount of Erythritol, in mg, taken to prepare the *Test solution;* r_i is the peak response for the *Test preparation;* and r_S is the response of the erythritol peak in the *Standard solution:* not more than 2.0% of any individual impurity is found, and not more than 2.0% of total impurities is found.

Assay—

Mobile phase—Use filtered and degassed 0.01% sulfuric acid.

Standard preparation—Dissolve an accurately weighed quantity of USP Erythritol RS in water to obtain a solution having a known concentration of about 50 mg per mL.

Assay preparation—Transfer 500 mg of Erythritol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

System suitability preparation—Transfer accurately weighed amounts of USP Erythritol RS and glycerol to a suitable volumetric flask, and dissolve in and dilute with water to obtain a solution having concentrations of about 0.05 mg per mL each.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 7.8-mm × 30-cm column or equivalent that contains packing L17. The flow rate is about 0.8 mL per minute. The column temperature is maintained at 70°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for erythritol and 1.1 for glycerol; and the resolution, R, between erythritol and glycerol 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 10 µL) each of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms over a period of three times the retention time of erythritol, and measure the peak responses. Calculate the amount, in mg, of $C_4H_{10}O_4$ in the portion of Erythritol taken by the formula:

$$VC(r_U/r_S)$$

in which V is the volume, in mL, of the *Assay preparation;* C is the concentration, in mg per mL, of USP Erythritol RS in the *Standard preparation;* and r_U and r_S are the peak responses for erythritol obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*NF24*)

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BRIEFING

Hydroxypropyl Cellulose, *NF 23* page 3017. It is proposed to delete *Identification* tests *A, B,* and *C* and to replace them with a single Fourier Transform IR test. In addition, it is proposed to add a *USP Reference standards* ⟨11⟩ section containing *USP Hydroxypropyl Cellulose RS.*

(EMC: J. Lane) RTS—42712-1

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Hydroxypropyl Cellulose RS.*■2S (*NF24*)

Change to read:

Identification—

~~**A:** Add about 1 g to 100 mL of water, previously heated to 60°, and stir: a slurry is formed that swells and disperses on cooling to form a colloidal solution.~~

~~**B:** Heat 10 mL of the solution prepared in *Identification* test *A* on a water bath while stirring: at a temperature of 45° the solution becomes cloudy, or a flocculant precipitate is formed, which disappears on cooling.~~

~~**C:** Place 1 mL of the solution prepared in *Identification* test *A* on a glass plate, and allow the water to evaporate: a thin, self sustaining film is formed.~~

■*Infrared Absorption* ⟨197K⟩.■2S (*NF24*)

BRIEFING

Isobutane, *NF 23* page 3021. It is proposed to delete the test for *Limit of sulfur compounds* because it is an odor test, and there are potential safety concerns.

(PA1: K. Russo) RTS—42915-3

Delete the following:

■~~**Limit of sulfur compounds**—Carefully open the container valve to produce a moderate flow of gas. Do not direct the gas stream toward the face, but deflect a portion of the stream toward the nose: the odor is free from the characteristic odor of sulfur compounds.~~■2S (*NF24*)

BRIEFING

Maltol, page 3358 of the *First Supplement*. It is proposed to revise the monograph to add a *Packaging and storage* section.

(EMC: D. Bempong) RTS—42704-1

Add the following:

■**Packaging and storage—**Preserve in tight containers, protected from light. No storage requirements specified.■2S (*NF24*)

BRIEFING

Monoethanolamine, *NF 23* page 3040. It is proposed to add a spectrophotometric identification test to this monograph employing *Infrared Absorption* ⟨197F⟩ and to include a new Reference Standard, USP Monoethanolamine RS, to be used to perform this test.

(EMC: C. Sheehan) RTS—42836-2

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Monoethanolamine RS.*■2S (*NF24*)

Add the following:

■**Identification,** *Infrared Absorption* ⟨197F⟩.■2S (*NF24*)

BRIEFING

Paraffin, *NF 23* page 3045. On the basis of comments received, it is proposed to revise the current test tube specifications as described in the test for *Readily carbonizable substances.*

(EMC: C. Sheehan) RTS—42641-1

Change to read:

Readily carbonizable substances ⟨271⟩—Use a clean, dry, heat-resistant, glass-stoppered test tube, ~~140 ± 3 mm in length and 14 ± 1 mm in diameter, with a capacity of 16 ± 1 mL when the stopper is inserted,~~

■140 ± 2 mm in length and between 14.5 and 15.0 mm in outside diameter,■2S *(NF24)* and calibrated at the 5- and 10-mL liquid levels.

■The capacity of the tube with stopper inserted is between 13.6 and 15.6 mL.[1]■2S *(NF24)* Place in the test tube 5 mL of Paraffin, at a temperature just above the melting point, add 5 mL of sulfuric acid containing 94.5% to 94.9% of H_2SO_4, and heat in a water bath at 70° for 10 minutes. When 5 minutes have elapsed, and at each successive minute thereafter, remove the tube from the bath, place a finger over the stopper, and give the tube three vigorous vertical shakes over an amplitude of about 12 cm, returning the tube to the bath within 3 seconds after the time when it was removed therefrom. At the end of 10 minutes from the time the tube was placed in the bath, the acid has no more color than a mixture of 3 mL of ferric chloride CS, 1.5 mL of cobaltous chloride CS, and 0.50 mL of cupric sulfate CS, overlaid with 5 mL of mineral oil. If the sulfuric acid remains dispersed in the molten paraffin, the color of the emulsion is not darker than that of the standard mixture when shaken vigorously.

BRIEFING

Potassium Alginate. Because there is no existing *NF* monograph for this article, a new monograph, based on the Potassium Alginate monograph in the *Food Chemicals Codex,* Fifth Edition, page 354 and the *Sodium Alginate* monograph in *NF 23,* page 3074, is being proposed.

(EMC: D. Bempong) RTS—42813-1

[1] A suitable test tube is available from Kimble Kontes. Item number: 34-19426. Description: Nessler Tube. Contact: phone 800-682-6644, fax 856-692-6644, customglass@kimkon.com.

Add the following:

■Potassium Alginate

Alginic acid, potassium salt.

Potassium alginate [*9005-36-1*].

» Potassium Alginate is the purified carbohydrate product extracted from various species of brown seaweeds by the use of dilute alkali. It consists chiefly of the potassium salt of Alginic Acid, a linear glycuronoglycan consisting of β-1,4 linked D-mannuronic acid and L-guluronic acid units in the pyranose ring form. It yields not less than 16.5 percent and not more than 19.5 percent of carbon dioxide (CO_2), equivalent to not less than 89.2 percent and not more than 105.5 percent of potassium alginate, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

Identification—

A: To 5 mL of a 1 in 100 solution in 0.1 N sodium hydroxide, add 1 mL of calcium chloride TS: a voluminous, gelatinous precipitate is formed.

B: To 10 mL of a 1 in 100 solution in 0.1 N sodium hydroxide, add 1 mL of 2 N sulfuric acid: a heavy, gelatinous precipitate is formed.

C: To about 5 mg in a test tube add 5 mL of water, 1 mL of a freshly prepared 1 in 100 solution of 1,3-naphthalenediol in alcohol, and 5 mL of hydrochloric acid. Heat the mixture to boiling, boil gently for 3 minutes, then cool to about 15°. Transfer the contents of the test tube to a 30-mL separator with the aid of 5 mL of water, and extract with

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15 mL of isopropyl ether: the isopropyl ether extract exhibits a deeper purplish hue than that from a blank, similarly prepared.

D: Ignite completely 0.2 g at as low a temperature as possible: a solution of the residue responds to the tests for *Potassium* ⟨191⟩.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 15% of its weight.

Total ash ⟨561⟩—Proceed as directed for *Total Ash* under *Methods of Analysis,* carefully igniting about 3 g, accurately weighed, in a tared platinum dish, until the residue is thoroughly carbonized (about 5 minutes), and then igniting in a muffle furnace at a temperature of 800 ±25° until the carbon is completely burned off (approximately 75 minutes): between 24.0% and 32.0% of ash is found, calculated on the as-is basis.

Arsenic, *Method II* ⟨211⟩**:** 1.5 µg per g.

Lead ⟨251⟩**:** Add 1.0 g to 20 mL of nitric acid in a 250-mL conical flask, mix, and heat carefully until the Potassium Alginate is dissolved. Continue the heating until the volume is reduced to about 7 mL. Cool rapidly to room temperature, transfer to a 100-mL volumetric flask, and dilute with water to volume. A 50.0-mL portion of this solution contains not more than 5 µg of lead (corresponding to not more than 0.001% of lead), 15 mL of ammonium citrate solution, 3 mL of potassium cyanide solution, and 0.5 mL of hydroxylamine hydrochloride solution being used for the test. After the first dithizone extractions, wash the combined chloroform layers with 5 mL of water, discarding the water layer and continuing in the usual manner by extracting with 20 mL of 0.2 N nitric acid.

Heavy metals, *Method II* ⟨231⟩—Conduct the ignition in a platinum crucible, and use nitric acid in place of sulfuric acid to wet the test specimen: the limit is 0.004%.

Assay—Proceed as directed under *Alginate Assay* ⟨311⟩.■2S (*NF24*)

BRIEFING

Trolamine, *NF 23* page 3103. It is proposed to revise the current *Identification* test by deleting the current *Identification* test *C* and replacing with a spectrophotometric *Identification* test *A* employing *Infrared Absorption* ⟨197F⟩. It is also proposed to include a new USP Reference Standard, USP Trolamine RS, to be used in *Identification* test *A*.

(EMC: C. Sheehan) RTS—42836-3

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Trolamine RS.*■2S (*NF24*)

Change to read:

Identification—

A: ~~To 1 mL add 0.1 mL of cupric sulfate TS: a deep blue color is produced. Add 5 mL of 1 N sodium hydroxide, and concentrate to one-third of the original volume by boiling: the blue color remains.~~

■*Infrared Absorption* ⟨197F⟩.■2S (*NF24*)

B: ~~To 1 mL add 0.3 mL of cobaltous chloride TS: a carmine-red color is produced~~

■To 1 mL add 0.1 mL of cupric sulfate TS: a deep blue color is produced. Add 5 mL of 1 N sodium hydroxide, and concentrate to one-third of the original volume by boiling: the blue color remains.■2S (*NF24*)

C: ~~Heat 1 mL gently in a test tube: the vapors turn moistened red litmus paper blue.~~

■To 1 mL add 0.3 mL of cobaltous chloride TS: a carmine-red color is produced.■2S (*NF24*)

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**1**〉 **Injections,** *USP 28* page 2201 and page 1149 of *PF* 31(4) [July–Aug. 2005]. The Parenteral Products—Industrial, Nomenclature and Labeling, and Safe Medication Use Expert Committees have agreed on the appearance of identifying numbers or letters on the side (skirt) surface of the ferrule on vials that contain injectable products. For the prevention of counterfeiting, an additional statement that allows any anti-counterfeit scheme to be present if it does not detract from or interfere with cautionary statements is included in the new proposed text for *Labeling on Ferrules and Cap Overseals.* The new text proposed in this *PF* under *In-Process Revision* will be targeted for the *Second Supplement* to *USP 29* with a 30-month delayed implementation date of February 1, 2009. The previous text for this section that appears in *USP 28* with an official date of October 1, 2005 is postponed indefinitely by a *Notice of Postponement* appearing in the *Fifth Interim Revision Announcement* also in this issue of *PF.*

(PPI: J. Kelly) RTS—42550-1

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Change to read:

LABELS AND LABELING

Labeling

NOTE—See definitions of "label" and "labeling" under *Labeling* in the section *Preservation, Packaging, Storage, and Labeling* of the *General Notices and Requirements.*

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

▪STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS

For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label followed in close proximity by strength per mL enclosed by parentheses. For containers less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL not mg/1 mL.

The following format would be acceptable for contents greater than 1 mL:

Total Strength/Total Volume: 500 mg/10 mL

Strength/mL: (50 mg/mL) or

Total Strength/Total Volume: 25,000 Units/5 mL

Strength/mL: (5,000 Units/mL)

The following format would be acceptable for contents less than 1 mL: 12.5 mg/0.625 mL

There are, however, some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be practical in preventing medication errors (e.g., insulin). An example is the use of lidocaine or other similar drugs used as a local anesthetic where the product is ordered and administered by percent (e.g., 1%, 2%) or a local anesthetic in combination with epinephrine which is expressed as a ratio (e.g., 1 : 100,000). In such cases, the total strength should be expressed (e.g., 1% (100 mg/10 mL). Dry solids, which need to be reconstituted, should follow the same format, with the exception that only the total strength of the drug is listed (not the strength/total volume or strength/mL).■2S (*USP29*)

(Official February 1, 2009)

~~Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition~~

~~(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (µg/L).~~

~~(b) The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per liter. This information must be contained in the "Precautions" section of the labeling of all large volume parenterals used in TPN therapy.~~

~~(c) The maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBPs) used in the preparation of TPN solutions. The aluminum content must be stated as follows: "Contains no more than ___ µg of aluminum per liter." The immediate container label of all SVPs and PBPs that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ____ µg per liter." This maximum level of aluminum must be stated as the highest of the following:~~

~~(1) The highest level for the batches produced during the last 3 years;~~

~~(2) The highest level for the latest five batches, or~~

~~(3) The maximum historical level, but only until completion of production of the first five batches after January 26, 2001.~~

~~(d) The package insert for all LVPs, all SVPs, and PBPs used in TPN must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling. The warning must state the following:~~

~~WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum.~~

~~Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.~~

▲Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy

(a) The aluminum content of LVIs used in TPN therapy must not exceed 25 µg per L.

(b) The package insert of LVIs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVIs used in TPN therapy.

(c) If the maximum amount of aluminum in SVIs and PBPs is 25 µg per L or less, instead of stating the exact amount of aluminum that each may contain, as in paragraph (d), the immediate container label for SVIs and PBPs used in the preparation or in the administration of TPN injections (with exceptions as noted below) and injectable emulsions may state: "Contains no more than 25 µg/L of aluminum." If the SVI or PBP is a lyophilized powder, the immediate container label may state the following; if the SVI or PBP is a lyophilized powder used in the preparation of TPN injections and injectable emulsions, the immediate container label must state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L."

(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVIs and PBPs used in the preparation or the administration of TPN injections and injectable emulsions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum." This maximum amount of aluminum may be stated as the highest one of the following three levels:

1. The highest level for the batches produced during the last three years,
2. The highest level for the latest five batches, or
3. The maximum level in terms of historical levels, but only until completion of production of the first five batches after the effective date of July 26, 2004.

The package insert for all LVIs, SVIs, and PBPs used in the preparation or administration of TPN products must contain a warning statement. This warning must be contained in the "Warnings" section of the labeling and must state the following: "WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions which contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products and of the lock-flush solutions used in their administration."▲*USP29*

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

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For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

(Official October 1, 2005)

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. The contents of up to five 1- or 2-mL containers may be pooled for the measurement, provided that a separate dry syringe assembly is used for each container. The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

~~Printing~~

■Labeling■2S (*USP29*)

on Ferrules and Cap Overseals

~~Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.~~

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~~The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.~~
~~(Official October 1, 2005)~~

■Only cautionary statements are to appear on the top (circle) surface of the ferrule or cap overseal of a vial containing an injectable product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements include but are not limited to the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", and "Chemotherapy".

The text must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may appear solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement beneath the cap to be readily legible.

Identifying numbers or letters, such as code numbers, lot numbers, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products. The appearance of such identifying data on the skirt surface of the ferrule, placed where it does not detract from, or interfere with, the cautionary statement on the top surface, should be considered to be a beneficial attribute of the in-process quality control of a product throughout the manufacturing process. Any anti-counterfeiting scheme must not detract from or interfere with the cautionary statements.

Under no circumstances would advertising such as company names, logos, or product names be permitted to appear on the top (circle) surface of any ferrule or cap overseal.■2S (*USP29*)

(Official February 1, 2009)

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

Change to read:

~~FOREIGN MATTER AND PARTICLES~~

▲FOREIGN AND PARTICULATE MATTER▲*USP29*

~~Foreign Matter~~

~~Every care should be exercised in the preparation of all products intended for injection to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents shows evidence of contamination with visible foreign material be rejected.~~

~~Particulate Matter~~

~~All large-volume Injections for single-dose infusion, and those small-volume Injections for which the monographs specify such requirements, are subject to the particulate matter limits set forth under *Particulate Matter in Injections* ⟨788⟩. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 ml or less if the individual monograph includes a test for *Particulate Matter*; it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter*.~~

▲All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in *Particulate Matter in Injections* ⟨788⟩ and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed "visible particulates") in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection

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process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container whose contents shows evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container–closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume injections for single-dose infusion and small-volume injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in *Particulate Matter in Injections* ⟨788⟩, unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume injection meets the requirements set forth for small-volume injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for *Particulate Matter in Injections* ⟨788⟩; it meets the requirements set forth for large-volume injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections administered exclusively by the intramuscular or subcutaneous route or packaged and labeled for use as irrigating solutions are exempt from requirements for *Particulate Matter in Injections* ⟨788⟩.▲*USP29*

BRIEFING

⟨**11**⟩ **USP Reference Standards,** *USP 28* page 2204, page 3557 of the *Second Supplement,* the *Third Interim Revision Announcement* on page 710 of *PF* 31(3) [May–June 2005], the *Fourth Interim Revision Announcement* on page 1017 of *PF* 31(4) [July–Aug. 2005], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], and page 1154 of *PF* 31(4) [July–Aug. 2005].

(HDQ) RTS—39091-2; 39091-3; 41078-2; 41977-2; 42281-1; 42281-2; 42596-1; 42623-1; 42677-1; 42709-1; 42836-1; 42836-2; 42836-3; 43019-1

Add the following:

■**USP Diclofenac Potassium RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Didanosine RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Didanosine Related Compound A RS**

[hypoxanthine**]**—[To come.]■2S (*USP29*)

Add the following:

■**USP Didanosine Related Compound B RS**

[2′,3′-dideoxyadenosine**]**—[To come.]■2S (*USP29*)

Add the following:

■**USP Didanosine System Suitability Mixture RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Diethanolamine RS**—Do not dry.■2S (*USP29*)

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Add the following:

■**USP Divalproex Sodium RS** [sodium hydrogen bis(2-propylvalerate), oligomer; pentanoic acid, 2-propyl-, sodium salt (2 : 1)] [$(C_{16}H_{31}NaO_4)_n$ ✧ 310.41]—[To come.]■2S (*USP29*)

Change to read:

~~**USP Ensulizole RS** [phyenylbenzimidazole sulfonic acid]—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■(NAME CHANGE) See *USP Phenylbenzimidazole Sulfonic Acid RS.*■2S (*USP29*)

Add the following:

■**USP Leflunomide RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Leflunomide Related Compound A RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Leflunomide Related Compound B RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Leflunomide Related Compound C RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Monoethanolamine RS**—Do not dry.■2S (*USP29*)

Add the following:

■**USP Norgestimate Related Compound A RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Norgestimate Oxime Mixture RS** [mixture of syn-17-deacetyl norgestimate and anti-17-deacetyl norgestimate]—[To come.]■2S (*USP29*)

Add the following:

■**USP Phenylbenzimidazole Sulfonic Acid RS**—Dry portion at 105° for 4 hours before using. Keep container tightly closed.■2S (*USP29*)

Add the following:

■**USP Pravastatin Sodium RS**—[To come.]■2S (*USP29*)

Add the following:

■**USP Pravastatin Related Compound A RS** [6α-hydroxyisocompactin sodium] or [sodium (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-3-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]heptanoate]—[To come.]■2S (*USP29*)

Add the following:

■**USP Prednicarbate RS**—Keep container tightly closed, protect from light, and store at controlled room temperature.■2S (*USP29*)

Add the following:

■**USP Prednicarbate Related Compound A RS** [1,2-dihydroprednicarbate]—Keep container tightly closed, protect from light, and store at controlled room temperature.■2S (*USP29*)

Delete the following:

~~■**USP Proinsulin (Beef) RS.**~~■2S (*USP29*)

Delete the following:

~~■**USP Proinsulin (Pork) RS.**~~■2S (*USP29*)

Add the following:

■**USP Trolamine RS**—Do not dry.■2S (*USP29*)

Add the following:

■**USP Tylosin Tartrate RS**—Dry portion in vacuum at 60° for 3 hours before using.■2S (*USP29*)

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BRIEFING

⟨**231**⟩ **Heavy Metals,** *USP 28* page 2299 and page 3295 of the *First Supplement.* On the basis of comments received, *Method II* is being revised to adequately address the issues resulting from the official publication of the revised *Method II* in the *First Supplement.* This proposed revision will not be the final solution to the issues related to *Method II,* but it will address the concerns of stakeholders at present. USP is working on developing a more robust method.

(PA6: K. Zaidi) RTS—42984-1; 42988-1

Change to read:

METHOD II

■NOTE—This method does not recover mercury.■1S (*USP28*)

pH 3.5 Acetate Buffer—Prepare as directed for *Method I.*

Standard Preparation—■Pipet 4 mL of the *Standard Lead Solution* into a suitable test tube, and add 10 mL of 6 N hydrochloric acid.■1S (*USP28*)

Test Preparation—Use a quantity, in g, of the substance to be tested as calculated by the formula:

■4.0/(1000*L*)■1S (*USP28*)

in which *L* is the heavy metals limit, ■as a■1S (*USP28*) 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.■1S (*USP28*) Cool, add ■5 mL■1S (*USP28*) of 6 N hydrochloric acid, cover, ■and■1S (*USP28*) digest on a steam bath for ■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.~~■1S (*USP28*)

■■2S (*USP29*)

Procedure—■Adjust the solution in■1S (*USP28*) each of the tubes containing the *Standard Preparation* ■■1S (*USP28*)

■and■2S (*USP29*)
the *Test Preparation* ■~~and the *Monitor Preparation*~~

■■2S (*USP29*)
with ammonium hydroxide, added cautiously and dropwise, to a pH of 9.

■Thoroughly mix the solution after each addition of ammonium hydroxide.■2S (*USP29*)
Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8, then add 0.5 mL in excess. Using a pH meter, ~~or short range pH indicator paper as external indicator, check the pH,and adjust,~~

■check and adjust the pH,■2S (*USP29*)
if necessary, with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 . Filter, if necessary, washing the filter with a few mL of water, into a 50-mL color-comparison tube, and then dilute with water to 40 mL.■1S (*USP28*) 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.]~~■1S (*USP28*)

■■2S (*USP29*)

BRIEFING

⟨**467**⟩ **Organic Volatile Impurities,** *USP 28* page 2322. It is proposed to change the chapter title to *Residual Solvents* and to delete the *Other Analytical Procedures* section (*Methods I, IV, V,* and *VI*). These proposals are consistent with revisions to individual monographs. The *Organic volatile impurities* ⟨467⟩ requirement will be deleted from all *USP, NF,* and *Dietary Supplements* monographs that currently contain it, and a new requirement for *Residual solvents* ⟨467⟩ will be added to all appropriate drug substance, excipient, drug product, and dietary supplement monographs. These individual monograph changes will appear in *USP 29–NF 24,* with a delayed implementation date of January 1, 2007.

Changes to the chapter text regarding submission of alternative methods to the USP are intended to clarify that these procedures will be reviewed by USP but will not necessarily be considered for incorporation into an individual monograph. Proposed changes to the chromatographic *Procedure* sections are intended to (1) compensate for possible matrix effects by providing spiked test solutions and (2) align the procedures with the composition of the Class 2 Residual Solvents Mixture Reference Standards.

In the absence of any significant adverse comment, it is proposed to implement these revisions via the *First Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of February 1, 2006, for the procedure changes and an official date of January 1, 2007, for the new chapter title and the deletion of the *Other Analytical Procedures* section.

(PA2: W. Paul) RTS—42665-1

Change to read:

⟨467⟩ ~~ORGANIC VOLATILE IMPURITIES~~

•RESIDUAL SOLVENTS•1

(Current title—not to change until January 1, 2007)
(Chapter title change—to become official January 1, 2007)

Change to read:

~~RESIDUAL SOLVENTS LIMITS~~

••1

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.

Change to read:

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 use in order to produce a medicinal product is unavoidable,•1
their levels should be restricted as shown in *Table 1,* unless otherwise stated in the individual monograph. The solvent 1,1,1-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 drug substance, 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.~~

•or produced in the manufacture or purification of a drug substance, excipient, or drug product, these solvents 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.•1
Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for ~~inclusion in the relevant individual monograph.~~

•evaluation.•1

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

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Class 2

Class 2 residual solvents *(Table 2)* should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the 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.~~

•evaluation.•

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~~

•quantification•
of these residual solvents. Such procedures shall be submitted to the USP for

•review and possible•
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
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
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
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
~~Trichloroethene~~	0.8	80
•Trichloroethylene•		
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 1*). 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,

•with appropriate modifications to the standard solutions,• 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.~~

•evaluation. USP Reference Standards, where available, should be used in these procedures.•

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.~~

••

Table 4. Other Residual Solvents
(for which no adequate toxicological data were found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent Hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Change to read:

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 appropriate headspace vial, add 5.0 mL of water, apply the 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.~~

•*Class 2 Standard Stock Solutions*—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the 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, add 1.0 mL of water, apply the stopper, cap, and mix.

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 the 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*

•*Mixture A*•
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*

•*Mixture A*•
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,*~~

•*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,*•
and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response 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,*~~

•either of the two *Class 2 Mixture Standard Solutions,*•

In-Process Revision

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~~

•*Solutions,*•
Class 2

•*Mixture A*•
Standard Solution,

•*Class 2 Mixture B Standard Solution,*•
Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

•*Class 2 System Suitability Solution*—Transfer 1.0 mL of USP Residual Solvent Class 2—Acetonitrile RS and 1.0 mL of USP Residual Solvent Class 2—Trichloroethylene RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the 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 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~~*

•*System Suitability*•
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;

•and•
the resolution, *R,* between acetonitrile and trichloroethylene in the *Class 2 ~~Standard~~*

•*System Suitability*•
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*

•*Mixture A*•
Standard Solution,

•the *Class 2 Mixture B 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

•either of•
the

•two•
Class 2

•*Mixture*•
Standard ~~Solution,~~

•*Solutions,*•
proceed to *Procedure C* to quantify the ~~peak~~

•peak(s);•
otherwise the article meets the requirements of this test.

Procedure C—

•*Class 1 Standard Stock Solution,*•
Class 1 Standard Solution,

•*Class 2 Standard Stock Solution A,*•
Class 2

•*Mixture A*•
Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—

•[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*]•
Transfer an accurately measured volume of ~~the~~

•each individual•
USP Reference Standard ~~for~~

•corresponding to•
each

•residual solvent•
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~~

•1/20•
of the value stated in *Table 1* or *2* (under *Concentration limit*). Transfer ~~5.0 mL~~

•1.0 mL•
of this solution to an appropriate headspace vial, add ~~1.0 mL~~

•5.0 mL•
of water, apply the stopper, cap, and mix.

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•*Spiked Test Solution*—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution,* apply the stopper, cap, and mix.•

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*

•*Mixture A*•
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*

•*Mixture A*•
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~~

•the•
Test Solution,

•and the *Spiked 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:

~~$4(C/W)(r_u/r_s)$~~

•$5(C/W)[r_U/(r_{ST} - r_U)]$•

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~~

•r_{ST}•
are the peak responses of each residual solvent obtained from the *Test Solution* and the ~~*Standard*~~

•*Spiked Test*•
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

•*A, Class 2 Standard Stock Solution B,*•
~~Class 2 Standard Solution,~~

•*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,*•
and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

•*Class 2 Standard Stock Solution C*—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture C RS to a 100-mL volumetric flask, dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.

Class 2 Mixture C Standard Solution—[NOTE—This solution is used for the identification and quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer 1.0 mL of *Class 2 Standard Stock Solution C* to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the 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 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 the stopper, cap, and mix.

Test Solution 2—

•[NOTE—These solutions are used for the identification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.]•
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 the 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,* ~~*Class 2 Standard Solution,*~~

•*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution,*•
Test Solution 1, and *Test Solution 2*

•(if applicable)•

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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,*~~

•any of the three *Class 2 Mixture Standard Solutions,*•1 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*

•*Mixture C*•1
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*~~

•*Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution,* and *Class 2 Mixture B Standard Solution*—•1
Prepare as directed for *Procedure A* under *Water-Soluble Articles.*

•*Class 2 Standard Stock Solution C, Class 2 Mixture C Standard Solution,*•1
Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

•*Class 2 System Suitability Solution* and•1
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,*~~

•*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution,*•1
Test Solution 1, and/or *Test Solution 2*

•(if applicable)•1
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

•any of•1
the ~~*Class 2 Standard Solution,*~~

•three *Class 2 Mixture Standard Solutions,*•1
proceed to *Procedure C* to quantify the ~~peak~~ •peak(s);•1
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*

•*Mixture C*•1
Standard Solution, proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

•*Class 1 Standard Stock Solution,*•1
Class 1 Standard Solution, Class 1 System Suitability Solution,

•*Class 2 Standard Stock Solution A,*•1
and *Class 2*

•*Mixture A*•1
Standard Solution—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

•*Standard Solution 1*—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with dimethylformamide to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Standard Solution 2—[NOTE—These solutions are used for the quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS and/or an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS to a suitable container; and dilute

quantitatively, and stepwise if necessary, with 1,3-dimethyl-2-imidazolidinone to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.•

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

•*Spiked Test Solution 1*—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 1,* apply the stopper, cap, and mix.

Spiked Test Solution 2—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Solution 2* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 2,* apply the stopper, cap, and mix.•

~~*Standard Solution,* and~~

••

Chromatographic System—Proceed as directed for *Procedure C* in *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,*

•and *Spiked Test Solution 1* and/or *Spiked 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:

~~$4(C/W)(r_U/r_S)$~~

$$•5(C/W)[r_U/(r_{ST} - r_U)]•$$

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~~

•r_{ST}•
are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and ~~*the Standard Solution,*~~

•*Spiked Test Solution 1* or *Spiked Test Solution 2,*•
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 performed on 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 (corresponding to 5000 ppm or 0.5% under *Option 1*), that residual solvent should be identified and quantified, and the procedures as described above,

•with appropriate modifications to the standard solutions,• 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.~~

•evaluation. USP Reference Standards, where available, should be used in these procedures.•
A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

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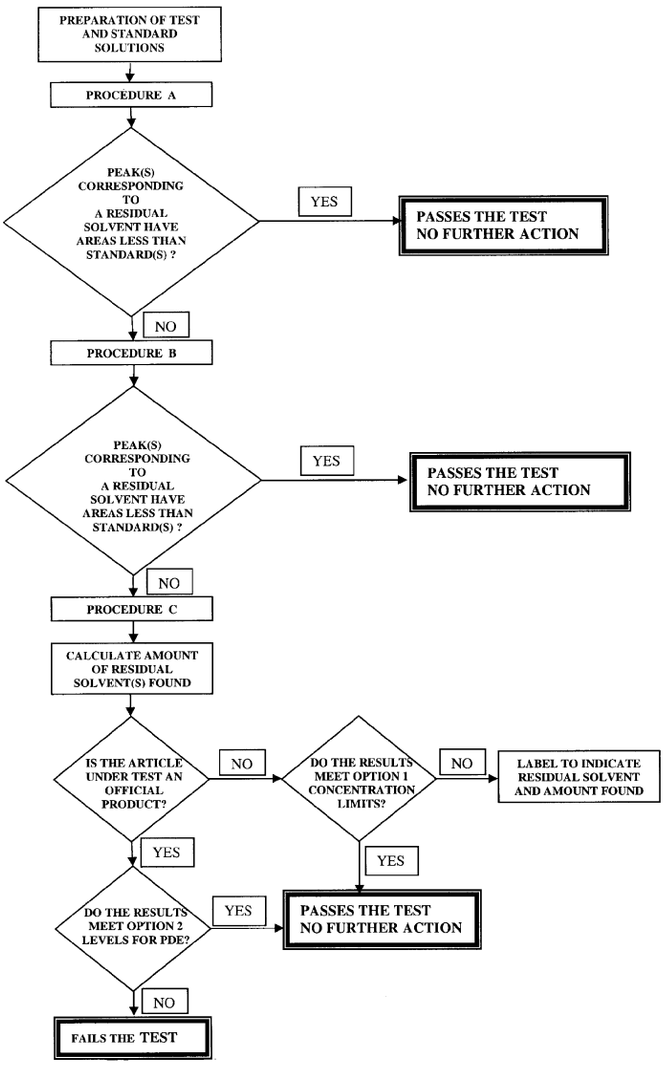

Fig. 1. Diagram relating to the identification of residual solvents and the application of limit tests.

In-Process Revision

Delete the following:

•~~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 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 injection port 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°

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~~**Table 6. Chromatographic Conditions for Method VI** *(Continued)*~~

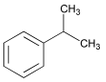
~~Chromatographic Conditions~~	~~USP Column Designation~~	~~Column Size~~	~~Column Temperature~~
~~F~~	~~S4~~	~~2 mm × 2.5 m~~	~~Hold 120° (35 min.)~~ ~~Gradient 120°–200°(2°/min.)~~ ~~Hold 20 min.~~
~~H~~	~~G14~~	~~2 mm × 2.5 m~~	~~Hold 45° (3 min.)~~ ~~Gradient 45°–120° (8°/min.)~~ ~~Hold 15 min.~~
~~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.~~

•1

•(Official January 1, 2007)•1

Change to read:

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
Cyclohexane	Hexamethylene		Class 2

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
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
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
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
Methylene chloride	Dichloromethane	CH_2Cl_2	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

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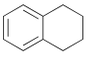
APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
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
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
~~Trichloroethene~~	1,1,2-Trichloroethene	$HClC{=}CCl_2$	Class 2
•Trichloroethylene•[1]			
Xylene*	Dimethybenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

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Physical Tests and Determinations

BRIEFING

⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions, page 2235 of *PF* 30(6) [Nov.–Dec. 2004]. This new general chapter, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision,* with proposed revisions based on comments received. Importantly, the mean size of lipid droplets must be submicron; and the population of large-diameter fat globules, expressed as the percentage of fat greater than 5 μm (i.e., PFAT5), must be kept at a minimum to avoid obstruction of the microvasculature, particularly the capillaries of the lungs. Therefore, these two regions of the globule size distribution (mean droplet size and large-diameter tail) must be controlled within specified limits.

It is proposed that two methods be employed for testing. *Method I* via classical (''Mie'') or dynamic light scattering will be designated for the mean diameter of the lipid droplets and for the range of the various droplet diameters distributed around the mean diameter, expressed as the standard deviation. *Method II,* light obscuration, will be designated for determining the amounts of fat globules composing the large-diameter tail of the globule size distribution. The revised chapter proposes universal limits for (1) mean droplet size not exceeding 500 nm or 0.5 μm and (2) the population of large-diameter fat globules, expressed as the volume-weighted percentage of fat great than 5 μm (PFAT5) not exceeding 0.05%, irrespective of the final lipid concentration.

(PPI: J. Kelly) RTS—42698-1

Add the following:

■⟨729⟩ GLOBULE SIZE DISTRIBUTION IN LIPID INJECTABLE EMULSIONS

INTRODUCTION

Lipid injectable emulsions used in total parenteral nutrition (TPN) therapy are sterile oil-in-water emulsions of soybean oil, used to provide an ample supply of essential fatty acids, linoleic and linolenic, dispersed with the aid of an emulsifying agent in *Water for Injection*. Alternatively, soybean oil can be mixed with other suitable oils (neutral triglycerides), such as safflower oil, medium-chain triglycerides (MCT) derived from coconut or palm kernel oils, olive oil, or a marine oil, such as menhaden oil. The size of the lipid droplets is critical: because of mechanical filtration, larger-size fat globules (> 5 μm) can be trapped in the lungs. The essential size characteristics of a lipid injectable emulsion for intravenous use includes the mean diameter of the lipid droplets and the range of the various droplet diameters distributed around the mean diameter, expressed as the standard deviation. In particular, the amounts of fat globules comprising the large-diameter tail of the globule size distribution are especially important with respect to infusion safety. These two regions of the globule size distribution (mean droplet size and large-diameter tail) must be controlled within specified limits.

The two methods described below are used for determination of the mean lipid droplet diameter and the distribution of large-diameter globule sizes in *Lipid Injectable Emulsion*. These methods must be employed for testing, following the requirements specified in the limits summarized in *Lipid Injectable Emulsion* (to come). *Method I* and *Method II* must be validated. The methods described below to assess the quality of lipid injectable emulsions are to be performed in two stages.

METHOD I—LIGHT-SCATTERING METHOD

For the determination of the mean droplet size of lipid injectable emulsions, either of two common light-scattering techniques may be employed: (1) dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), or (2) classical light scattering, based on Mie scattering theory. The DLS, or PCS, technique is based on analyzing the rapid temporal fluctuations in the scattered light intensity that occur due to the random Brownian motion, or diffusion, of any particles, including lipid droplets, sus-

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pended in liquid. The intensity is measured at a given angle (usually 90°) by a suitable detector (e.g., photomultiplier tube) able to measure the rapidly fluctuating scattered light intensity produced by the suspended, diffusing droplets. These scattered intensity data are typically used to calculate the intensity autocorrelation function, which is a simple decaying exponential function in time for droplets of uniform size. A distribution of droplet sizes expresses itself by exponential functions of different decay times. The autocorrelation function generated by the scattered intensity data obtained from a given emulsion can be ''inverted'' by means of an appropriate deconvolution algorithm in order to obtain the approximate distribution of intensity-weighted diffusion coefficients. From the latter, the distribution of small-diameter droplets is calculated, using the Stokes-Einstein equation and the rules of classical (Mie) light scattering.

By contrast, classical light scattering based on Mie theory analyzes the spatial, rather than temporal, variation of the scattered light intensity by measuring the latter as a function of the scattering angle, typically over a large range of detected angles. The temporal fluctuations in the scattering intensity due to Brownian motion are averaged out in time for each angular measurement. This angular variation occurs as a consequence of the mutual interference of individual scattered waves arriving at the detector with different phases from different points within a given lipid droplet, as well as from different particles. The extent of the angular variation is significant whenever the droplet diameter is not small compared with the wavelength of the laser light (typically 635 nm). Droplets of a given size and refractive index yield a unique curve of scattering intensity vs. angle. A distribution of droplet sizes gives rise to a final angular dependence that represents the superposition, or summation, of individual (different) intensity vs. angle curves. The measured angular dependence of the scattering intensity obtained from a given emulsion sample can be inverted by means of an appropriate deconvolution algorithm and Mie scattering theory in order to obtain the approximate droplet size distribution.

Thus, light scattering, using either dynamic light scattering (i.e., temporal fluctuations due to droplet diffusion) or classical light scattering/Mie theory (i.e., average intensity vs. angle), can provide acceptable results for both the mean diameter and standard deviation of the droplet size distribution. For purposes of illustrating the method used in *Method I,* a dynamic light-scattering technique is described. For guidance regarding instruments employing classical Mie-theory light scattering, see *Light Diffraction Measurement of Particle Size* ⟨429⟩.

Apparatus—A suitable DLS/PCS instrument with or without the capability of automatic sample dilution is controlled by validated software and is used to perform the measurement, with the scattering angle typically set at 90°. The intensity-weighted results (mean diameter and standard deviation) are reported, provided it is clearly stated which values are given and that the necessary parameter values required for all requisite calculations are also given.

Water—Pass distilled water through a filter having a 0.2-µm porosity, and degas by sonication, or use *Sterile Water for Injection* stored in a glass container.

Standard Preparation—To a pre-established volume of *Water* add an appropriate amount of concentrated suspension, containing NIST-traceable polystyrene latex standard particles or other suitable nanospheres. Gently mix the fluids to achieve a homogeneous suspension. The diluted suspension will be slightly turbid in appearance. If the DLS/PCS instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe, with further dilution occurring automatically to optimize the

droplet concentration for analysis. Alternatively, the sample would require greater manual dilution with *Water* (typically by at least a factor of 10 over the first dilution), and then this sample would be instilled into a "drop-in" cuvette. The optimum dilution scheme that achieves the proper scattering intensity for the cuvette-based analysis will be determined by the instrument specifications. Thus, the concentration of latex in the final sample must be optimized for the DLS/PCS instrument used. This should be performed separately for three different size standards of approximately 100, 250, and 400 nm (triplicate analyses per size), and the corresponding results of intensity-weighted mean diameter and standard deviation should coincide with the expected values within acceptable errors.

Test Preparation—To a pre-established volume of *Water* add an appropriate volume of sample from the lipid injectable emulsion. Gently mix the fluids to achieve a homogeneous suspension. The diluted suspension will be slightly turbid in appearance. Gently mix the fluids. If the DLS/PCS instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe. Further dilution of the sample then occurs automatically to optimize the droplet concentration for analysis, ensuring that it is not so high as to cause artifacts due to multiple scattering or interdroplet interactions. Alternatively, the sample would require greater manual dilution with water (typically by at least a factor of 10 over the first dilution), and then this sample would be instilled into a "drop-in" cuvette. The optimum dilution scheme that achieves the proper scattering intensity for the cuvette-based analysis will be determined by the instrument specifications. Thus, the concentration of lipid injectable emulsion in the final sample must be optimized for the DLS/PCS instrument used.

System Suitability—Using the *Standard Preparation,* measure the intensity-weighted mean particle diameter and the corresponding standard deviation. The system is suitable once the sample temperature has reached equilibration and the results have stabilized and triplicate mean droplet diameter measurements are obtained. ~~within 15% of each other.~~ The coefficient of variation (CV) should not exceed ~~20%~~ 10% of the NIST-traceable mean droplet diameter. A larger CV value indicates that the latex microspheres are not suitable as a standard because they either inherently lack uniformity or have become agglomerated to an unacceptable extent. In this case, another standard latex suspension must be selected and tested.

Procedure and Interpretation—If the DLS/PCS instrument is equipped with an automatic dilution system, use a disposable syringe to load the *Standard Preparation* or *Test Preparation*. If no automatic dilution system is used, transfer the appropriately diluted preparation to a cuvette and place the cuvette in the spectrometer. Allow the sample to equilibrate to a preset controlled temperature close to ambient (between 20° and 25°, as in the USP definition found in the *General Notices* under *Preservation, Packaging, Storage, and Labeling*). Set the instrument scattering angle to 90°, and carry out the measurements. As long as the chi-square (χ^2) goodness-of-fit parameter remains acceptably low (per instrument specifications), the results for the *Test Preparation* are acceptable. Excessive values of the χ^2 parameter suggest that the droplet distribution is not normal and may indicate an unstable emulsion. The intensity-weighted mean droplet diameter (MDD) for lipid injectable

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emulsions ~~of various concentrations must be met:~~ must be less than 500 nm or 0.5 μm, irrespective of the concentration of the dispersed lipid phase.

~~Concentration of Dispersed Phase (% w/v)~~			
	~~10~~	~~20~~	~~30~~
~~MDD (nm)~~	~~<300~~	~~<400~~	~~<500~~

METHOD II—~~LIGHT OBSCURATION OR EXTINCTION METHOD~~ MEASUREMENT OF LARGE GLOBULE CONTENT BY LIGHT OBSCURATION OR EXTINCTION METHOD

For determination of the extent of the large-diameter droplet tail (>5 μm) of lipid injectable emulsions a light obscuration (LO) or light extinction (LE) method that employs a single-particle (globule) optical sizing (SPOS) technique is used. During application of the LE/SPOS technique, passage of a droplet through a thin optical sensing zone results in blockage of a portion of the incident light beam, causing a momentary decrease in the light intensity reaching the "extinction" detector. The magnitude of this decrease in the signal is ideally proportional to the cross-sectional area of the droplet (assumed smaller than the sensing zone thickness), i.e., to the square of the droplet diameter. During optimization of the LE/SPOS instrument for a given emulsion sample, a series of dilutions should be tested to achieve an acceptably low coefficient of variation (i.e., <10%) between samples. The goal is to identify a standard range of dilutions that yield consistent data and are most applicable to the formulation tested. Ideally, when comparing different emulsions, the same approximate number of globules are sized each time, and once a standard is achieved, it should be incorporated into the routine sampling plan for validation testing. As long as the fat globule concentration is below the "coincidence limit" of the sensor (determined by the flow cell and optical design), only one globule at most will pass through the sensing zone at any given time, allowing it to be counted and accurately sized (with less than 1% coincidence events). Both the coincidence limit and the optimal flow rate must be known for the LE/SPOS sensor used. Furthermore, it is prudent to perform the large-diameter measurements at a reduced emulsion concentration such that the measurable droplet concentration (i.e., >1.8 μm) is only approximately one-third of the nominal coincidence limit for the sensor used. The resulting single pulse heights are converted to droplet diameters using a standard calibration curve previously constructed from NIST-traceable monosized polystyrene microspheres of known diameters. For additional guidance in the use of the light obscuration methodology, see the general chapter *Particulate Matter in Injections* ⟨788⟩.

Apparatus—A suitable light obscuration instrument with or without the capability of automatic sample dilution and controlled by a personal computer (PC) is used for the measurement. The number- and volume-weighted particle size distribution data are reported, provided it is clearly stated which values are given and that the necessary parameter values required for all necessary calculations are also given.

Water—Pass distilled water through a filter having a 0.2-μm porosity, and degas by sonication, or use *Sterile Water for Injection* stored in a glass container.

Standard Preparation—To a pre-established volume of *Water* add an appropriate amount of concentrated suspension, containing NIST-traceable polystyrene latex standard particles or other suitable microspheres. Gently mix the fluids to achieve a homogeneous suspension. If the light obscuration instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe or Teflon sample line. Further dilution of the sample

then occurs automatically to optimize the particle concentration for analysis. Alternatively, the sample would require greater manual dilution with water (typically by at least a factor of 10 over the first dilution). The resulting diluted sample is then instilled in an appropriate, clean container, such as a sterile Type I glass container, before being passed through the sensor. In either case the final particle concentration is caused to lie below the coincidence limit of the sensor. The sizing and counting accuracy of the light obscuration instrument should be obtained using three different size standards of approximately 5 µm, 10 µm, and 25 µm (triplicate analyses per size). The corresponding results for the mean diameter should coincide with the expected values, within a 10% acceptable error. In addition, the number of particle counts obtained per unit volume of diluted sample suspension should also agree, within a 10% acceptable error, with the concentration values certified in the documentation provided with each NIST-traceable size standard.

Test Preparation—To a pre-established volume of *Water* add an appropriate volume of sample from the lipid injectable emulsion. Gently mix the fluids to achieve a homogeneous suspension. The diluted emulsion will be slightly turbid in appearance. If the light obscuration instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe or nonreactive* Teflon sample line. Further dilution then occurs automatically to optimize the droplet/globule concentration for analysis. Alternatively, the sample would require greater manual dilution with water (typically by at least a factor of 10 over the first dilution). The resulting diluted sample is then instilled in an appropriate, clean container such as a sterile Type I glass container. In either case the final droplet/globule concentration is caused to lie below the coincidence limit of the sensor.

System Suitability—Using the *Standard Preparation,* measure the number-weighted particle diameter and the corresponding standard deviation. The system is suitable once the sample has equilibrated and the results have stabilized and triplicate mean number-weighted particle diameter measurements are obtained within 10% of each other. The measured coefficient of variation (CV) for the number-weighted particle size distribution should not deviate by more than 25% from the CV value stipulated for the NIST-traceable standard. The latter value is usually very small, assuming nearly uniform-size standard particles. Therefore, in practice the measured CV value is usually considerably larger than this ideal value, being dictated instead by the resolution of the LE/SPOS sensor. The resolution of the sensor should be sufficiently good that the measured CV value does not exceed 15% of the mean diameter of the NIST-traceable standard. A larger CV value indicates that the latex microspheres are not suitable as a standard because they either inherently lack uniformity or have become agglomerated to an unacceptable extent. In this case, another standard latex suspension must be selected and tested.

Procedure and Interpretation—If the light obscuration instrument is equipped with an automatic dilution system, use a disposable syringe or Teflon sample line to load the *Standard Preparation* or *Test Preparation.* If no automatic dilution system is used, transfer the sample to an appropriate large-volume, clean container such as a sterile Type I glass vessel containing an appropriate volume of *Water.* Allow the sample and *Water* to mix thoroughly to achieve a homogeneous suspension. Set the instrument threshold of detection at 1.8 µm, extended to an upper limit of 50 µm, and employ measurement times of 120, 180, and 240 seconds

* Polyvinyl chloride (PVC) with diethylhexylphthalate (DEHP) has been shown to induce breakdown of lipid injectable emulsions (Drug Product Problem Reporting System. USP File Access No. 11173, May 15, 1991).

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for each run of each replicate of the sample (n = 3 runs per sample). As long as the three measurements of the volume-weighted percentage of fat greater than 5 µm (PFAT5) for each sample fall within 10% of each other (irrespective of run time), the results for the *Test Preparation* are acceptable. Values exceeding this reproducibility tolerance suggest either that the sample is unstable or that the dilution has not been optimized. The volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 µm (PFAT5) for a given lipid injectable emulsion, must be less than 0.05%.■2S (*USP29*)

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1058**⟩ **Analytical Instrument Qualification,** page 1157 of *PF* 31(4) [July–Aug. 2005]. On the basis of comments received, it is proposed to revise this text in order to reflect current practices. In addition, minor editorial changes have been made.

(PA4: H. Pappa) RTS—42634-1; 42645-1; 41668-1; 42737-1

Add the following:

■⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of instruments and tools, ranging from simple nitrogen evaporators to complex multiple-function technologies, are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use. ~~and that they do not pose high safety risks~~ The analyst's objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures and perform system suitability tests and in-process quality control checks to help ensure that the acquired data are reliable. These activities help enhance the quality of data, and there are specific guidances and procedures for performing these activities. With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions abound regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification, approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data. Note that a risk-based approach to provide flexibility in the qualification process, commensurate with the complexity and intended use of the instrumentation, is acceptable.

Validation versus Qualification

Because there is ambiguity in the use of the terms "validation" and "qualification", in this chapter the term "validation" will be used for processes and software, and the term "qualification" will be used for instruments. Thus, the phrase "analytical instrument qualification" (AIQ) is used for the process of ensuring that an instrument is suit-

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able for its intended application. The term "validation" is reserved for processes including analytical procedures and software procedures.

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the base for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control checks. These quality components are described below.

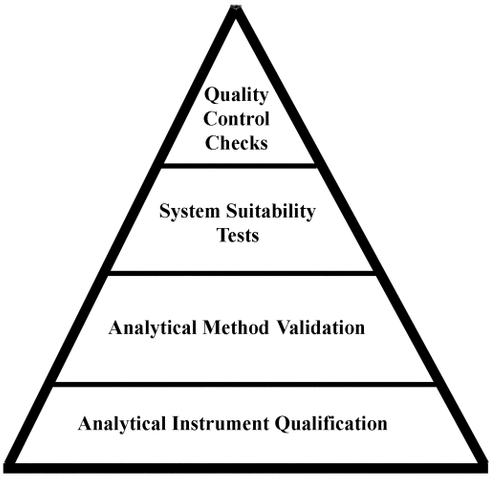

Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure does what it purports to do and addresses the required attributes of the procedure. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality. Users of compendial procedures perform validation using the criteria provided in general information chapter *Validation of Compendial Methods* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform according to the analyst's expectations and according to the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. USP general chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests.

Quality Control Checks

Most analyses are performed on instruments calibrated or standardized using reference materials or calibration standards. The calibration or standardization process uses a single- or multiple-point calibration, depending on the instrument and the intended application. The calibration or standardization of an instrument during analysis ensures

that the instrument response correlates with the known quantity or quality of the calibration standard or reference material. In addition to calibration or standardization, some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance.

The extent of system suitability tests or quality control checks varies for different analyses, depending on their intended use. Chemical analyses, which are largely subject to Good Manufacturing Practices (GMP) regulations and require tighter precision and accuracy, may require more system suitability tests than bioanalytical work, which is largely subject to Good Laboratory Practice (GLP) regulations. Bioanalytical work requires sensitive, specific, broad-range analysis and therefore is generally performed with more quality control checks during sample analysis. Control check samples are also appropriate when high-variability tests or instruments (i.e., those with a relative standard deviation [RSD] higher than 5%) are considered. Other use-specific considerations may also determine the extent of system suitability tests or quality-control-check sample analysis. Whatever the case, the sum total of such controls provides an important step in delivering quality data for the intended purpose.

In summary, analytical instrument qualification and analytical method validation ensure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks ensure the quality of analytical results *immediately before* or *during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical data—analytical method validation, system suitability tests, and quality control checks—are not within the scope of this chapter.

Qualification Phases

Instrument qualification is not a single continuous process, but instead results from several discrete activities. For convenience, these activities can be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Some of these qualification terms have their roots in manufacturing-process validation. Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Also, some AIQ activities cover more than one qualification phase and could arguably be performed within any of the phases. It is important that the required AIQ activities be performed; however, within which qualification phase an activity is performed or reported is not as important. *Table 1* accommodates these overlapping activities by letting users perform them under one or another phase as necessary. The user should describe where the activity is performed and reported.

Table 1. Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification*

DQ	IQ		OQ		PQ
Timing and applicability					
Prior to purchase of a new type of instrument	At installation of each instrument (new, old, or existing unqualified)		After installation or major repair of each instrument		Periodically at specified intervals for each instrument
Activities					
Assurance of vendor's DQ	System description	⇆	Fixed parameters		Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery				SOPs for operation, calibration, maintenance and change control
Instrument's fitness for use in laboratory	Utilities/facility/environment				
	Network and data storage	⇆	Secure data storage, backup, and archive		
	Assembly and installation				
	Installation verification	⇆	Instrument function tests	⇆	Performance checks

* Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Such activities spanning more than one qualification phase are shown as connected by double arrows. If an activity listed under a given phase is performed under another phase, it is not necessary to repeat the activity under the phase where the activity is listed. Performing the activity is far more important than the phase under which the activity is performed.

DESIGN QUALIFICATION

Design qualification (DQ) is most suitably performed by the instrument developer or manufacturer. Because the instrument design is already in place for commercial off-the-shelf (COTS) systems, users do not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature of the instrument, the complexity of the proposed application, and the extent of the user's previous interaction with the manufacturer. Vendor audits or required vendor-supplied documentation satisfy part of the DQ requirements. The required scope and comprehensiveness of the audits and documentation vary with users' familiarity with the instrument and their previous interactions with the vendor.

Informal processes also form an important part of DQ. Informal personal communications and networking with peers at technical or user-group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Informal site visits to other users' and vendors' facilities to obtain data on representative samples that used the specified instrument are another good source of information about suitability for intended use. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection.

INSTALLATION QUALIFICATION

Installation qualification (IQ) is the documented collection of activities necessary for installing an instrument in the user's environment. IQ applies to an instrument that is new or was pre-owned, or to any instrument that exists on site but has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been packed and transported to another location. The activities and documentation associated with IQ are as follows.

System Description—Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flow charts where appropriate.

Instrument Delivery—Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment—Verify that the installation site satisfactorily meets vendor-specified environmental requirements. A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.

Network and Data Storage—Some analytical systems require users to provide network connections and data storage capabilities at the installation site. When required, connect the instrument to the network, and check its functionality.

Assembly and Installation—Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor, specialized engineers, or qualified in-house personnel,* whereas users can assemble and install simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. If the pre-owned, unqualified existing instrument or transported instrument requires assembly and installation, perform the tasks as specified above, then perform the installation verification procedure, described below.

Installation Verification—Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and, when present, the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

OPERATIONAL QUALIFICATION

After a successful IQ, the instrument is ready for OQ testing. The OQ phase may consist of these test parameters.

Fixed Parameters—These tests measure the instrument's nonchanging parameters such as length, height, weight, voltage inputs, acceptable pressures, and loads. If the ven-

dor-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need redetermination. [NOTE—These tests could also be performed during the IQ phase (see *Table 1*); if so, fixed parameters need not be redetermined as part of OQ testing.]

Secure Data Storage, Backup, and Archiving—When required, test secure data handling such as storage, backup, and archiving at the user's site according to written procedures.

Instrument Function Tests—Important instrument functions should be tested to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter. Nevertheless, as a guide to the types of tests possible during OQ, consider the following, which apply to an HPLC unit:

- pump flow rate
- gradient linearity
- detector wavelength accuracy
- detector linearity
- column oven temperature
- injector precision and accuracy
- peak retention time precision

Routine analytical tests do not constitute OQ testing. OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment, and repeating the testing at regular intervals may not be required. However, when the instrument undergoes major repairs or modifications, relevant OQ tests should be repeated to verify whether the instrument continues to operate satisfactorily. Relevant OQ tests should also be repeated for an instrument that has been transported to another location, although a move within the laboratory, or from one room to another, that does not disturb instrument operation may not require requalification.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification. ~~and should be performed whenever possible.~~ Holistic tests, which involve the entire system, are also acceptable. ~~in lieu of modular testing.~~ Having successfully completed OQ testing, the instrument is qualified for use in regulated samples analysis.

PERFORMANCE QUALIFICATION

After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through performance qualification (PQ). The PQ phase includes the following parameters.

Performance Checks—Set up a test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications~~. Some~~ and may consist of analyzing known components or standards. The tests should be based on good science and reflect the general intended use of the instrument. These tests may resemble those performed during OQ, but the specifications for their results

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can be set differently if required. ~~PQ tests should be performed routinely on a working instrument, not only on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications.~~ Nevertheless, user specifications for PQ tests should evince trouble-free instrument operation for the intended applications. ~~PQ tests should be performed independently of the routine analytical testing performed on the instrument.~~ As is the case with OQ testing, PQ tests can be modular or holistic. However, because many modules within a system interact, holistic tests generally prove to be more effective because they evaluate the entire system, not simply the system's individual modules.

Testing frequency depends on the ruggedness of the instrument and the criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. It may also be scheduled for regular intervals, such as weekly or monthly. Experience with the instrument can influence this decision. ~~Generally, the same PQ tests are repeated~~ It may be useful to repeat the same PQ tests each time so that a history of the instrument's performance can be compiled. Alternatively, the instrument may be incorporated into an integrated support system to assure that it remains continually qualified. Some system suitability tests or quality control checks that are performed concurrently with the test samples also imply that the instrument is performing suitably. ~~However, although system suitability tests can supplement periodic PQ tests, they cannot replace them.~~

Preventive Maintenance and Repairs—When an instrument fails to meet PQ test specifications, it requires maintenance or repair. A periodic preventive maintenance may also be recommended for many instruments. The relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Standard Operating Procedure[s] for Operation, Calibration, ~~and~~ Maintenance and Change Control—Establish standard operating procedures to maintain and calibrate the instrument. ~~Use a logbook, binder, or electronic record to document each~~ Each maintenance and calibration activity should be documented.

Roles and Responsibilities

USERS

Users are ultimately responsible for instrument operations and data quality. The user's group encompasses analysts, their supervisors, and organization management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments, because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, validation specialists, and quality assurance (QA) personnel can advise and assist as needed, but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

QUALITY ASSURANCE

The QA role in AIQ remains the same as for any other regulated study. QA personnel should understand the instrument qualification process, and they should learn about the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it

meets regulatory requirements, and they should make certain that the users attest to the scientific validity of the process.

MANUFACTURERS

Manufacturers and developers are responsible for DQ when designing the instrument. They are also responsible for validation of relevant processes used in manufacturing and assembly of the hardware and for software associated with the instrument. Manufacturers and developers are also responsible for writing stand-alone software for analytical work in a documented quality manner and for the validation of this software. Manufacturers should test the assembled instruments before shipping them to users.

Manufacturers and vendors should make available to users a summary of their validation efforts and the results of final instrument and software tests, and they should provide the critical functional test scripts that can be used to qualify the instrument and software at the user site. For instance, manufacturers and vendors can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, manufacturers and vendors should notify all known users about hardware or software defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

SOFTWARE VALIDATION

Software used for analytical work can be classified into three categories: firmware; instrument control, data acquisition, and processing software; and stand-alone software.

Firmware—Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users generally cannot alter firmware design or function. Firmware is therefore considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware. Thus, when the hardware (that is, the analytical instrument) is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see *Change Control,* below).

Instrument Control, Data Acquisition, and Processing Software—Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and postacquisition calculations. Thus both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire instrument and software system, is more efficient than modular validation of the software alone. Thus the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process.

Stand-Alone Software—An authoritative guide for validating stand-alone software, such as LIMS, is available.[1] The validation process is administered by the software developer, who also specifies the development model appropriate for the software. Validation takes place in a series of activities planned and executed through various stages of the development cycle.

The software validation guide cited in the previous paragraphs indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only part of the validation process for stand-alone software and does not constitute complete validation. Refer to the software validation guide for activities that must be performed at the user site for testing stand-alone software used in analytical work.

Change Control

Changes to the instrument and software become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required. The change control process enables them to do this.

Change control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below:

Operational Qualification—Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.

Performance Qualification—Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In the future, perform the revised PQ testing.

For changes to firmware and to software for instrument control, data acquisition, and processing, change control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change control for stand-alone software requires user-site testing of changed functionality.

AIQ Documentation

Two types of documents result from AIQ: static and dynamic.

STATIC DOCUMENTS

Static documents are obtained during the DQ, IQ, and OQ phases and should be ~~kept in a "Qualification" binder~~ retained in an accessible manner. Where multiple instruments of one kind exist, documents common to all instruments ~~should go into one binder or section,~~ and documents specific to an instrument ~~should go into that instrument's binder or section~~ may be retained separately. During change control, additional documents ~~can be placed with~~ may supplement

[1] *General Principles of Software Validation: Final Guidance for Industry and FDA Staff,* U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, January 11, 2002. http://www.fda.gov/cdrh/comp/guidance/938.html (accessed September 2004).

the static ones, but previous documents should not be ~~removed~~ discarded. When necessary, such documents may be archived.

DYNAMIC DOCUMENTS

Dynamic documents are generated during the OQ and PQ phases when the instrument is maintained or tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them. These documents ~~may~~ should also be archived as necessary.

Instrument Categories

Modern laboratories typically include a suite of tools varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of principles to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Examples of instruments in each group are provided. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site. That category should be determined by users for their specific instruments or applications.

GROUP A

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Examples of instruments in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, water baths, and glass pipets.

GROUP B

Conformance of Group B instruments to user requirements is determined according to an instrument's standard operating procedures. Conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple, and causes of their failure are readily discernible by simple observation. Examples of instruments in this group are balances, incubators, ~~IR spectrometers,~~ melting point apparatus, muffle furnaces, light microscopes, pH meters, variable pipets, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, and viscosimeters.

GROUP C

Conformance of Group C instruments to user requirements is complex and highly method-specific; conformity bounds are determined by the application. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Examples of instruments in this group include the following:

- atomic absorption spectrometers
- differential scanning calorimeters
- electron microscopes
- flame absorption spectrometers
- high-pressure liquid chromatographs
- mass spectrometers
- microplate readers
- thermal gravimetric analyzers

- X-ray fluorescence spectrometers
- X-ray powder diffractometers
- densitometers
- diode-array detectors
- elemental analyzers
- gas chromatographs
- IR spectrometers
- near IR spectrometers
- Raman spectrometers
- UV/Vis spectrometers
- inductively coupled argon–plasma emission spectrometers

Again, it must be emphasized that the placement of these instruments in the given three groups is for illustrative purposes only. The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

CONCLUSION

The purpose of the use of analytical instruments is to generate reliable data. Analytical instrument qualification helps fulfill this purpose. No authoritative guide existed that considered the risk of instrument nonperformance and combined that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments became a subjective and often fruitless document-generating exercise.

This chapter is based on the outcome of a user workshop-conference on the subject and provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The process provided in this chapter focuses on scientific value rather than on producing documents. Implementing such a process should increase efficiency and remove ambiguous or varying interpretations by different groups.■2S (*USP29*)

BRIEFING

⟨1092⟩ The Dissolution Procedure: Development and Validation, page 351 of *PF* 30(1) [Jan.–Feb. 2004]. This proposed new general information chapter, which previously appeared in *Pharmacopeial Previews,* is now forwarded with changes to *In-Process Revision.* The chapter provides several needed types of information. Currently, aspects of method development are mentioned only superficially in the general information chapter *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩; the present chapter goes into greater detail and gives guidance to the analyst on developing meaningful dissolution methods. Similarly, the general information chapter *Validation of Compendial Methods* ⟨1225⟩ touches only on special considerations for validation of dissolution testing, whereas this proposed chapter provides a typical detailed step-by-step approach to designing and validating a dissolution test. Last, this new general information chapter provides guidance to the analyst on validation and the use of new technologies and equipment in dissolution testing. The chapter is loosely based on a stimuli article, "A New General Information Chapter on Dissolution," by V.A. Gray, C.K. Brown, J.B. Dressman, and L.J. Leeson that appeared on page 3432 of *PF* 27(6) [Nov.–Dec. 2001]. The information provided here was revised, in part, on the basis of comments from experts in the pharmaceutical industry. The participation of the PhRMA Dissolution Expert Team is gratefully acknowledged.

(BPC: W. Brown) RTS—42981-1

Add the following:

■⟨1092⟩ THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

The USP dissolution procedure is a performance test applicable to many dosage forms. It is one test in a series of tests that constitute the dosage form's public specification (tests, procedures for the tests, acceptance criteria). To satisfy the performance test, USP provides the general test chapters *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, and *Drug*

Release ⟨724⟩. These chapters provide information about conditions of the procedure. For dissolution, these include information about (1) medium, (2) apparatus/agitation rate, (3) study design, (4) assay, and (5) acceptance criteria. Overall the dissolution procedure yields data to allow an accept/reject decision relative to the acceptance criteria, which are frequently based on a regulatory decision. This chapter provides recommendations on how to develop and validate a dissolution procedure.

GENERAL COMMENTS

The dissolution procedure requires an apparatus, a dissolution medium, and test conditions that provide a method that is discriminating yet sufficiently rugged and reproducible for day-to-day operation and capable of being transferred between laboratories.

The acceptance criteria should be representative of multiple batches with the same nominal composition and manufacturing process, typically including key batches used in pivotal studies, and representative of performance in stability studies.

The procedure should be appropriately discriminating, capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. It is also possible for the procedure to show differences between batches when no significant difference is observed in vivo. This situation requires careful evaluation of whether the procedure is too sensitive or appropriately discriminating. Assessing the results from multiple batches that represent typical variability in composition and manufacturing parameters may assist in this evaluation. It is sometimes valuable to intentionally vary manufacturing parameters, such as lubrication, blend time, compression force, or drying parameters, to further characterize the discriminatory power of the procedure.

With regard to stability, the dissolution test should appropriately reflect relevant changes in the drug product over time that are caused by temperature, humidity, photosensitivity, and other stresses.

A properly designed test should result in data that are not highly variable and should not be associated with significant analytical solution stability problems. High variability in results can make it difficult to identify trends or effects of formulation changes. Dissolution results may be considered highly variable if the relative standard deviation (RSD) is greater than 20% at time points of 10 minutes or less and greater than 10% RSD at later time points.[1] However, most dissolution results exhibit less variability than this. The source of the variability should be investigated when practical and attempts should be made to reduce variability whenever possible. The two most likely causes are the formulation itself (e.g., drug substance, excipients, or manufacturing process) or artifacts associated with the test procedure (e.g., coning, tablets sticking to the vessel wall or basket screen). Visual observations are often helpful for understanding the source of the variability and whether the dissolution test itself is contributing to the variability. Any time the dosage contents do not disperse freely throughout the vessel in a uniform fashion, aberrant results can occur. Depending on the problem, the usual remedies include changing the apparatus type, speed of agitation, or deaeration; consideration and/or examination of sinker type; and changing the composition of the medium. Modifications to the apparatus may also be useful, with proper justification and validation.

[1] The Biopharmaceutics Classification System is outlined in the FDA *Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System,* August 2000; http://www.fda.gov/cder/guidance/3618fnl.htm, accessed 6/22/2005.

Many causes of variability can be found in the formulation and manufacturing process. For example, poor content uniformity, process inconsistencies, a reaction taking place at different rates during dissolution, excipient interactions or interference, film coating, capsule shell aging, and hardening or softening of the dosage form on stability may be sources of variability and interferences. During routine testing of the product, variability outside the expected range should be investigated from analytical, formulation, and processing perspectives.

MEDIUM

Physical and chemical data for the drug substance and dosage unit need to be determined before selecting the dissolution medium. Two key properties of the drug are the solubility and solution state stability of the drug as a function of the pH value. When selecting the composition of the medium, the influence of buffers, pH value, and surfactants on the solubility and stability of the drug need to be evaluated. Key properties of the dosage unit that may affect dissolution include release mechanism (immediate, delayed, or modified) and disintegration rate as affected by hardness, friability, presence of solubility enhancers, and presence of other excipients.

Generally, when developing a dissolution procedure, one goal is to have *sink conditions,* defined as the volume of medium at least three times that required in order to form a saturated solution of drug substance. When sink conditions are present, it is more likely that dissolution results will reflect the properties of the dosage form. A medium that fails to provide sink conditions may be acceptable if it is shown to be more discriminating or otherwise appropriately justified.

Using an aqueous–organic solvent mixture as a dissolution medium is discouraged; however,with proper justification this type of medium may be acceptable.

Purified water is often used as the dissolution medium, but is not ideal for several reasons. First, the quality of the water can vary depending on the source of the water, and the pH value of the water is not controlled. Second, the pH value can vary from day to day and can also change during the run, depending on the active substance and excipients. Despite these limitations, water is inexpensive, readily available, easily disposed of, ecologically acceptable, and suitable for products with a release rate independent of the pH value of the medium.

The dissolution characteristics of an oral formulation should be evaluated in the physiologic pH range of 1.2 to 6.8 (1.2 to 7.5 for modified-release formulations). During method development, it may be useful to measure the pH before and after a run to discover whether the pH changes during the test. Selection of the most appropriate conditions for routine testing is then based on discriminatory capability, ruggedness, stability of the analyte in the test medium, and relevance to in vivo performance, where possible.

Typical media for dissolution may include the following (not listed in order of preference): dilute hydrochloric acid, buffers in the physiologic pH range of 1.2 to 7.5, simulated gastric or intestinal fluid (with or without enzymes), water, and surfactants (with or without acids or buffers) such as polysorbate 80, sodium lauryl sulfate, and bile salts.

The molarity of the buffers and acids used can influence the solubilizing effect, and this factor may be evaluated.

For compounds with high solubility and high permeability (as defined by the Biopharmaceutics Classification System), the choice of medium and apparatus may be influenced by the referenced FDA Guidance[1].

For very poorly soluble compounds, aqueous solutions may contain a percentage of a surfactant (e.g., sodium lauryl sulfate, polysorbate, or lauryldimethylamine oxide) that is used to enhance drug solubility. The need for surfactants and the concentrations used can be justified by showing profiles at several different concentrations. Surfactants can be used either as wetting agents or to solubilize the drug substance.

Volume

Normally, for basket and paddle apparatus, the volume of the dissolution medium is 500 mL to 1000 mL, with 900 mL as the most common volume. The volume can be raised to between 2 and 4 L, using larger vessels and depending on the concentration and sink conditions of the drug; justification for this procedure is expected.

Deaeration

The significance of deaeration of the medium should be determined, because air bubbles can interfere with the test results, acting as a barrier to dissolution if present on the dosage unit or basket mesh. Further, bubbles can cause particles to cling to the apparatus and vessel walls. On the other hand, bubbles on the dosage unit may increase buoyancy, leading to an increase in the dissolution rate, or may decrease the available surface area, leading to a decrease in the dissolution rate. A dearation method is described as a footnote in the *Procedure* section under *Dissolution* ⟨711⟩. Typical steps include heating the medium, filtering, and drawing a vacuum for a short period of time. Other methods of deaeration are available and in routine use throughout the industry. Media containing surfactants are not usually deaerated because the process results in excessive foaming. To determine whether deaeration of the medium is necessary, results from dissolution samples run in nondeaerated medium and deaerated medium should be compared.

Enzymes

The use of enzymes in the dissolution medium is permitted in accordance with *Dissolution* ⟨711⟩ when dissolution failures occur as a result of cross-linking with gelatin capsules or gelatin-coated products.

In Vitro–In Vivo Correlation (IVIVC)

An in-depth discussion on IVIVC can be found in *In Vitro and In Vivo Evaluation of Dosage Forms* ⟨1088⟩. A brief discussion follows.

Biorelevant medium is a medium that has some relevance to the in vivo performance of the dosage unit. Choice of a biorelevant medium is based on (1) a mechanistic approach that considers the absorption site, if known, and (2) whether the rate-limiting step to absorption is the dissolution or permeability of the compound. In some cases, the biorelevant medium will be different from the test conditions chosen for the regulatory test, and the time points are also likely to be different. If the compound dissolves quickly in the stomach and is highly permeable, gastric emptying time may be the rate-limiting step to absorption. In this case, the dissolution test should demonstrate that the drug is released quickly under typical gastric (acidic) conditions. On the other hand, if dissolution occurs primarily in the intestinal tract (e.g., for a poorly soluble, weak acid), a higher pH range (e.g., simulated intestinal fluid with a pH of 6.8) may be more appropriate. The fed and fasted states may also have significant effects on the absorption or solubility of a compound. Compositions of media that simulate the fed and fasted states can be found in the literature. These media reflect changes in

pH, bile concentrations, and osmolarity after meal intake and therefore have a composition different from that of typical compendial media. They are primarily used to establish in vitro–in vivo correlations during formulation development and to assess potential food effects and are not intended for quality control purposes. For quality control purposes, the substitution of natural surfactants (bile components) with appropriate synthetic surfactants is permitted and encouraged because of the expense of the natural substances and the labor-intensive preparation of the biorelevant media.

APPARATUS/AGITATION

Apparatus

The choice of apparatus is based on knowledge of the formulation design and the practical aspects of dosage form performance in the in vitro test system. For solid oral dosage forms, *Apparatus 1* and *Apparatus 2* are used most frequently.

When *Apparatus 1* or *2* is not appropriate, another official apparatus may be used. *Apparatus 3 (Reciprocating Cylinder)* has been found to be especially useful for bead-type modified-release dosage forms. *Apparatus 4 (Flow-Through Cell)* may offer advantages for modified-release dosage forms that contain active ingredients with limited solubility. In addition, *Apparatus 3* or *Apparatus 4* may have utility for soft gelatin capsules, bead products, suppositories, or poorly soluble drugs. *Apparatus 5 (Paddle* over *Disk)* and *Apparatus 6 (Rotating Cylinder)* have been shown to be useful for evaluating and testing transdermal dosage forms. *Apparatus 7 (Reciprocating Holder)* has been shown to have application to nondisintegrating oral modified-release dosage forms, as well as to transdermal dosage forms.

Some changes can be made to the apparatus; for example, a basket mesh size other than the typical 40-mesh basket (e.g., 10, 20, 80 mesh) may be used when the need is clearly documented by supporting data. In countries where available mesh sizes vary from the USP specified mesh value, basket material with the nearest metric dimension should be used. Care must be taken that baskets are uniform and meet the dimensional requirements specified under *Dissolution* ⟨711⟩. If the basket screens become clogged during dissolution of capsule or tablet formulations, it may be advisable to switch to the paddle method. The volume can be increased from the typical 900 to 1000 mL by using 2- and 4-L vessels to assist in meeting sink conditions for poorly soluble drugs.

A noncompendial apparatus may have some utility with proper justification, qualification, and documentation of superiority over the standard equipment. For example, a small-volume apparatus with mini paddles and baskets may be considered for low-dosage strength products. The rotating bottle or static tubes (jacketed stationary tubes enclosed with a water jacket and equipped with a magnetic stirrer) may also have utility for microspheres and implants, peak vessels for eliminating coning, and modified flow through cells for special dosage forms, including powders and stents.

Sinkers

When sinkers are used, a detailed description of the sinker must be stated in the written procedure. It may be useful to evaluate different sinkers, recognizing that sinkers can significantly influence the dissolution profile of a dosage unit. When transferring the procedure, the sinkers should be duplicated as closely as possible in the next facility. There are several types of commercially available sinkers. A method

for making sinkers by hand, sinkers that are similar to "a few turns of wire helix" as described in *Apparatus 2 (Paddle Apparatus)* under *Dissolution* ⟨711⟩, is described below.

Materials—Use 316 stainless steel wire or other inert material, typically 0.032 inch/20 gauge; and cylinders of appropriate diameter (e.g., cork borers). Sizes are shown in the table.

Capsule Shell Type	Length of Wire (cm)	Diameter Size (cm)	Cork Bore Number
#0, elongated	12	0.8	4
#1 and #2	10	0.7	3
#3 and #4	8	0.55	2

Procedure—Cut the specified length of wire, coil around a cylinder of the appropriate size, and use small pliers to curve in the ends. Use caution, because wire ends may be rough and may need to be filed.

If the sinker is handmade, the sinker material and construction procedure instructions should be documented; if a commercial sinker is used, the vendor part number should be reported.

Agitation

For immediate-release capsule or tablet formulations, *Apparatus 1* (baskets) at 100 rpm or *Apparatus 2* (paddles) at 50 or 75 rpm are most commonly used. Other agitation speeds and apparatus are acceptable with appropriate justification.

Rates outside 25 to 150 rpm are usually inappropriate because of the inconsistency of hydrodynamics below 25 rpm and because of turbulence above 150 rpm. Agitation rates between 25 and 50 rpm are generally acceptable for suspensions. For dosage forms that exhibit coning (mounding) under the paddle at 50 rpm, the coning can be reduced by increasing the paddle speed to 75 rpm, thus reducing the artifact and improving the data. If justified, 100 rpm may be used, especially for extended-release products. Decreasing or increasing the apparatus rotation speed may be justified if the profiles better reflect in vivo performance and/or the method results in better discrimination without adversely affecting method reproducibility.

Selection of the agitation and other study design elements for modified-release dosage forms is similar to that for immediate-release products. These elements should conform to the requirements and specifications given in *Dissolution* ⟨711⟩ when the apparatus has been appropriately calibrated.

STUDY DESIGN

Time Points

For immediate-release dosage forms, the duration of the procedure is typically 30 to 60 minutes; in most cases, a single time point specification is adequate for Pharmacopeial purposes. Industrial and regulatory concepts of product comparability and performance may require additional time points, which may also be required for product registration or approval. A sufficient number of time points should be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the Biopharmaceutics Classification System referred to in several FDA Guidances, highly soluble, highly permeable drugs formulated with rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release 85% or more of the active drug substance within 15 minutes. For these types of products a one-point test will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products typically show a gradual increase reaching 85% to 100% at

about 30 to 45 minutes. Thus, dissolution time points in the range of 15, 20, 30, 45, and 60 minutes are usual for most immediate-release products. For rapidly dissolving products, including suspensions, useful information may be obtained from earlier points, e.g., 5 to 10 minutes. For slower-dissolving products, time points later than 60 minutes may be useful. Dissolution test times for compendial tests are usually established on the basis of an evaluation of the dissolution profile data.

So-called infinity points can be useful during development studies. To obtain an infinity point, the paddle or basket speed is increased at the end of the run for a sustained period (typically 15 to 60 minutes), after which time an additional sample is taken. Although there is no requirement for 100% dissolution in the profile, the infinity point can provide data that may supplement content uniformity data and may provide useful information about formulation characteristics during initial development or about method bias.

For an extended-release dosage form, at least three test time points are chosen to characterize the in vitro drug release profile for Pharmacopeial purposes. Additional sampling times may be required for drug approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that there is little probability of dose dumping. An intermediate time point is chosen to define the in vitro release profile of the dosage form, and a final time point is chosen to show the essentially complete release of the drug. Test times and specifications are usually established on the basis of an evaluation of drug release profile data. For products containing more than a single active ingredient, drug release is to be determined for each active ingredient.

Observations

Visual observations and recordings of product dissolution and disintegration behavior are very useful because dissolution and disintegration patterns can be indicative of variables in the formulation or manufacturing process. To accomplish visual observation, proper lighting (with appropriate consideration of photodegradation) of the vessel contents and clear visibility in the bath are essential. Documenting observations by drawing sketches and taking photographs or videos can be instructive and helpful for those who are not able to observe the real time dissolution test. Observations are especially useful during method development and formulation optimization. Examples of typical observations include, but are not limited to, the following:

1. Uneven distribution of particles throughout the vessel. This can occur when particles cling to the sides of the vessel, when there is coning or mounding directly under the apparatus, when particles float at the surface of the medium, when film-coated tablets stick to the vessel, and/or when off-center mounds are formed.
2. Air bubbles on the inside of the vessel or on the apparatus or dosage unit. Sheen on the apparatus is also a sign of air bubbles. This observation would typically be made when assessing the need to deaerate the medium.
3. Dancing or spinning of the dosage unit, or the dosage unit being hit by the paddle.
4. Adhesion of particles to the paddle or the inside of the basket, which may be observed upon removal of the stirring device at the end of the run.
5. Pellicles or analogous formations, such as transparent sacs or rubbery, swollen masses surrounding the capsule contents.

6. Presence of large floating particles or chunks of the dosage unit.
7. Observation of the disintegration rate (e.g., percentage reduction in size of the dosage unit within a certain time frame).
8. Complex disintegration of the coating of modified or enteric-coated products—for example, the partial opening and splitting apart (like a clamshell) or incomplete opening of the shell accompanied by the release of air bubbles and excipients.

Sampling

Manual—Manual sampling uses plastic or glass syringes, a stainless steel cannula that is usually curved to allow for vessel sampling, a filter, and/or a filter holder. The sampling site must conform to specifications under *Dissolution* ⟨711⟩.

Autosampling—Autosampling is a useful alternative to manual sampling, especially if the test includes several time points. However, because regulatory labs may perform the dissolution test using manual sampling, autosampling requires validation with manual sampling.

There are many brands of autosamplers, including semi-automated and fully automated systems. Routine performance checks, cleaning, and maintenance as described in the pertinent standard operating procedures or metrology documents are useful for reliable operation of these devices.

Some instruments are equipped with sampling through the basket or paddle shaft. Proper validation (e.g., demonstrated equivalence to results with the usual sampling procedure) may be required.

The disturbance of the hydrodynamics of the vessel by sampling probes should be considered and adequate validation performed to ensure that the probes are not introducing a significant change in the dissolution rate.

Comparison of manual and automated procedures should be performed to evaluate the interchangeability of the procedures. This can be accomplished by comparing data from separate runs or, in some cases, by sampling both ways from the same vessel. Results should be consistent with the requirements for intermediate precision (described in this chapter in *Validation*) if the procedures are to be considered interchangeable.

Other aspects of automation validation may include carryover of residual drug, effect of an in-residence probe (simultaneous sampling as mentioned above may not be suitable in this case), adsorption of drug, and cleaning and/or rinse cycles.

Filters

Filtration of the dissolution samples is usually necessary to prevent undissolved drug particles from entering the analytical sample and further dissolving. Also, filtration removes insoluble excipients that may otherwise cause high background or turbidity. Prewetting of the filter with the medium may be necessary.

Filters can be in-line or at the end of the sampling probe or both. The pore size can range from 0.45 to 70 μm. The usual types of filters are depth, disk, and flow-through. However, if the excipient interference is high, if the filtrate has a cloudy appearance, or if the filter becomes clogged, an alternative type of filter or pore size should be evaluated.

Adsorption of the drug(s) onto the filter needs to be evaluated. If drug absorption occurs, the amount of initial filtrate discarded may need to be increased. If results are still unsuitable, an alternative filter material may be sought.

Filter validation may be accomplished by preparing a suitable standard solution or a completely dissolved sample solution (e.g., prepared as a typical sample in a vessel or a sample put in a beaker and stirred with a magnetic stirrer for 1 hour). For standard solutions, compare the results for filtered solutions (after discarding the appropriate volume) to those for the unfiltered solutions. For sample solutions, compare the results for filtered solutions (after discarding the appropriate volume) to those for centrifuged, unfiltered solutions.

Centrifugation

Centrifugation of samples is not preferred, because dissolution can continue to occur and because there may be a concentration gradient in the supernatant. A possible exception might be for compounds that adsorb onto all common filters.

ASSAY

The usual assay for a dissolution sample is either spectrophotometric determination or HPLC. The preferred method of analysis is spectrophotometric determination because results can be obtained faster, the analysis is simpler, and fewer solvents are used. HPLC methods are used when there is significant interference from excipients or among drugs in the formulation to improve analytical sensitivity and/or when the analysis can be automated. It may be useful to obtain data for the drug with a stability-indicating assay (e.g., HPLC chromatograms) in the medium of choice, even if the primary assay is based on a spectrophotometric method.

VALIDATION

The validation topics described in this section are typical but not all-inclusive. The validation elements addressed may vary, depending on the phase of development or the intended use for the data.[2] The acceptance criteria are presented as guidelines only and may differ for some products. Firms should document the appropriate acceptance criteria for their products in pertinent SOPs. Other considerations may be important for special dosage forms. The extent of validation depends on the phase of the product development. Full validation takes place by the time of Phase III clinical studies. Validation studies should address the variations associated with different profile time points. For products containing more than a single active ingredient, the dissolution method needs to be validated for each active ingredient.

Specificity/Placebo Interference

It is necessary to demonstrate that the results are not unduly affected by placebo constituents, other active drugs, or degradates.

The placebo consists of all the excipients and coatings (inks, sinker, and capsule shell are also included when appropriate) without the active ingredient. Placebo interference may be determined by weighing samples of the placebo blend and dissolving or dispersing them in dissolution medium at concentrations that would be encountered during testing. It may be desirable to perform this experiment at 37° by comparing it to the 100% standard by the formula:

$$100C(A_P / A_S)(V/L)$$

in which C is the concentration, in mg per mL, of the standard; A_P and A_S are the absorbances of the placebo and the

[2] Boudreau, S.P., McElvain, J.S., Martin, L.D., Dowling, T., Fields, S.M. Method Validation by Phase of Development, an Acceptable Analytical Practice. *Pharmaceutical Technology* 2004; 28(11):54–66.

standard, respectively; V is the volume, in mL, of the medium; and L is the label claim, in mg. The interference should not exceed 2%.

NOTE—For extended-release products, a placebo version of the finished dosage form may be more appropriate to use than blends, because this placebo formulation will release the various excipients in a manner more nearly reflecting the product than will a simple blend of the excipients. In this case, it may be appropriate to evaluate potential interference at multiple sampling points in the release profile.

If the placebo interference exceeds 2%, then method modification—such as (1) choosing another wavelength, (2) baseline subtraction using a longer wavelength, or (3) using HPLC—may be necessary in order to avoid the interference. When other active drugs or significant levels of degradates are present, it is necessary to demonstrate that these do not significantly affect the results. One procedure for doing this is to measure the matrix in the presence and absence of the other active drug or degradate: any interference should not exceed 2%.

Linearity and Range

Linearity and range are typically established by preparing solutions of the drug, ranging in concentration from below the lowest expected concentration to above the highest concentration during release. This may be done in conjunction with accuracy/recovery determination. The scheme may be altered if different flow-cell sizes or injection volumes are used.

Typically, solutions are made from a common stock if possible. For the highest concentration, the determination may not exceed the linearity limits of the instrument.

Organic solvents may be used to enhance drug solubility for the preparation of the standard solutions; however, no more than 5% (v/v) of organic solvent in the final solution should be used, unless validated.

Linearity is typically calculated by using an appropriate least-squares regression program. Typically, a square of the correlation coefficient ($r^2 \geq 0.98$) demonstrates linearity. In addition, the y-intercept must not be significantly different from zero.

Accuracy/Recovery

Accuracy/recovery are typically established by preparing multiple samples containing the drug and any other constituents present in the dosage form (e.g., excipients, coating materials, capsule shell) ranging in concentration from below the lowest expected concentration to above the highest concentration during release.

In cases of poor drug solubility, it may be appropriate to prepare a stock solution by dissolving the drug substance in a small amount of organic solvent (typically not exceeding 5%) and diluting to the final concentration with dissolution medium. An amount of stock solution equivalent to the targeted label claim may be added to the vessel instead of the drug powder. Similarly, for very low strengths, it may be more appropriate to prepare a stock solution than to attempt to weigh very small amounts. The measured recovery is typically 95% to 105% of the amount added. Bracketing or matrixing of multiple strengths may be useful.

A special case for validation is the *Acid Stage* procedure described in *Delayed-Release Dosage Forms* under *Dissolution* ⟨711⟩. The limit of not more than 10% needs to be validated. If the compound degrades in acid, the validation experiment must address this fact.

Precision

Repeatability—Repeatability is determined by replicate measurements of standard and/or sample solutions. It can be measured by calculating the RSD of the multiple injections or spectrophotometric readings for each standard solution, or from the accuracy or linearity data.

Intermediate Precision—Intermediate precision may be evaluated to determine the effects of random events on the precision of the analytical procedure. This evaluation is typically done later in the development of the drug product. The precision can be across the range of product strengths. Typical variations to study include days, analysts and equipment. The use of an experimental matrix design is encouraged for evaluation of intermediate precision. If possible, intermediate precision can be evaluated using a well-characterized lot of drug product of tight content uniformity. In cases where a well-characterized product is not available, placebo and active ingredient may be used to identify intermediate precision.

The dissolution profiles on the same sample may be run by at least two different analysts, each analyst preparing the standard solutions and the medium. Typically, the analysts use different dissolution baths, spectrophotometers or HPLC equipment (including columns), and autosamplers; and they perform the test on different days. This procedure may not need to be performed for each strength; instead, bracketing with high and low strengths may be acceptable.

A typical acceptance criterion is that the difference in the mean value between the dissolution results at any two conditions using the same strength does not exceed an absolute 10% at time points with less than 85% dissolved and does not exceed 5% for time points above 85%. Acceptance criteria may be product specific, and other statistical tests and limits may be used.

Robustness

The evaluation of robustness, which assesses the effect of making small, deliberate changes to the dissolution conditions, typically is done later in the development of the drug product. The number of replicates (typically 3 or 6) is dependent on the intermediate precision.

Parameters to be varied are dependent on the dissolution procedure and analysis type. They may include medium composition (e.g., buffer or surfactant concentration), pH, volume, agitation rate, and temperature. For HPLC analysis, parameters may include mobile phase composition (percentage organic, buffer concentration, pH), flow rate, wavelength, column temperature, and multiple columns (of the same type). For spectrophotometric analysis, the wavelength may be varied.

Standard and Sample Solution Stability

The standard solution is stored under conditions that ensure stability. The stability of the standard is analyzed over a specified period of time, using a freshly prepared standard solution at each time interval for comparison. The acceptable range for standard solution stability is typically between 98% and 102%.

The sample solution is typically stored at room temperature. The sample is analyzed over a specified period of time using the original sample solution response for comparison. The typical acceptable range for sample solution stability may be between 98% and 102% compared with the initial analysis of the sample solutions. If the solution is not stable, aspects to consider could be temperature (refrigeration may be needed), light protection, and container material (plastic or glass).

The procedure may state that the standards and samples need to be analyzed within a time period demonstrating acceptable standard and sample solution stability.

Spectrophotometric Analysis

Samples may be automatically introduced into the spectrophotometer using autosippers and flow cells. Routine performance checks, cleaning, and maintenance as described in the standard operating procedures or metrology documents are useful for reliable operation of these instruments. Cells with path lengths ranging from 0.02 to 1 cm are typically used. Cell alignment and air bubbles could be sources of error. The smaller path length cells are used to avoid diluting the sample; however, acceptable linearity and standard error need to be demonstrated.

During analysis, standard solutions are typically prepared and analyzed at just one concentration at 100% (or the selected *Q* value) of the dosage strength. During profile analysis, other concentrations may be useful. A typical blank, standard, and sample may be analyzed in a sequence that brackets the sample with standards and blanks, especially at the beginning and end of the analysis.

In most cases, the mean absorbance of the dissolution medium blank may not exceed 1% of the standard. Values higher than 1% must be evaluated on a case-by-case basis. The typical RSD for UV analysis is usually not more than 2%.

The absorptivity is calculated by dividing the mean standard absorbance by the concentration, in mg per mL, divided by the flow-cell path length in cm. After enough historical data are accumulated, an acceptable absorptivity range for the analyte (using the appropriate flow cell) may be determined. This value may be useful in troubleshooting aberrant data.

Fiber optics as a sampling and determinative method, with proper validation, is an option.

It may be useful to examine the UV spectrum of the drug in solution to select the optimum wavelength.

HPLC

For HPLC analysis, the compatibility of dissolution media and mobile phase may be examined, especially if large injector volumes (over 100 µL) are needed. Samples are normally analyzed with HPLC using a spectrophotometric detector and an autoinjector. Single injections of each vessel time point with standards throughout the run constitute a typical run design. System suitability tests include, at a minimum, the retention window and injection precision. Typically, the repeatability of an HPLC analysis should be less than or equal to 2% RSD for five or six standard determinations. The standard level is typically at the 100% label claim level, especially for a single-point analysis.

Preparation of the placebo samples for the HPLC analysis is to be performed in the same way as in the spectrophotometric analysis. Examine the chromatogram for peaks eluting at the same retention time as the drug. If there are extraneous peaks, inject the standard solution, and compare retention times. If the retention times are too close, spike the placebo solution with the drug. Chromatograms may also be obtained over an extended run time using the blank (dissolution medium), standard, and sample solution to identify late eluters that may interfere with subsequent analyses.

The validation documentation may include overlaid representative chromatograms or spectra of blank dissolution medium, a filtered placebo solution, a standard solution, and a filtered dissolution sample. Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity.

ACCEPTANCE CRITERIA

Typical acceptance criteria for the amount of active ingredient dissolved, expressed as a percentage of the labeled content *(Q),* are in the range of 75% to 80% dissolved. A *Q* value in excess of 80% is not generally used, because allowance needs to be made for assay and content uniformity ranges.[3] Acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Acceptance criteria should be consistent with historical data, and there is an expectation that acceptable batches (e.g., no significant differences in in vivo performance, composition, or manufacturing procedure) will have results that fall within the acceptance criteria.■2S (*USP29*)

BRIEFING

⟨1223⟩ Validation of Alternative Microbiological Methods, page 256 of *PF* 29(1) [Jan.–Feb. 2003]. On the basis of comments received, it is proposed to rewrite this general information chapter. The qualitative and quantitative aspects will form the content of the proposed chapter, while the section on identification has been removed.

(AMB: R. Tirumalai) RTS—43020-1

Add the following:

■⟨1223⟩ VALIDATION OF ALTERNATIVE MICROBIOLOGICAL METHODS

INTRODUCTION

~~Microbiological testing laboratories sometimes use test methods other than those described in the general chapters for microbial recovery and identification for a variety of reasons such as economics, higher throughput, and convenience. Validation of these substitute methods is required. The *Tests and Assays* section in the *General Notices and Requirements* provides some guidance on the validation of alternate methods, citing that the method under consideration must provide an advantage in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or other special circumstances. The section also notes that in the event of a dispute, only the result obtained by the compendial test is conclusive.~~

~~Proposed alternative tests must be adequately validated. General information chapter *Validation of Compendial Methods* ⟨1225⟩ provides guidance on the validation of chemical assays proposed for adoption as compendial assays. It is the purpose of this general information chapter to provide guidance on the demonstration of the suitability of alternative microbiological methods to be used as part of, or in lieu of, compendial assays.~~

~~The purpose of this chapter is to provide guidance for the validation of methods for use as alternatives to official compendial microbiological methods. For microbial recovery and identification, microbiological testing laboratories sometimes use alternative test methods to those described in the general chapters for a variety of reasons such as economies, throughput, and convenience. Validation of these methods is required. Some guidance on validation is provided in the *Tests and Assays* section in the *General Notices and Requirements* on the use of alternative methods. The section also notes that in the event of a dispute, only the result obtained by the compendial test is conclusive.~~

The purpose of this chapter is to provide guidance for validating methods for use as alternatives to the official compendial microbiological methods. For microbial recovery and identification, microbiological testing laboratories

[3] See the FDA Guidance for Industry: *Dissolution Testing of Immediate-Release Solid Oral Dosage Forms,* August 1997; http://www.fda.gov/cder/guidance/1713bp1.pdf, accessed 6/22/2005.

sometimes use alternative test methods to those described in the general chapters for a variety of reasons, such as economics, throughput, and convenience. Validation of these methods is required. Some guidance on validation is provided in the *Tests and Assays* section in the *General Notices and Requirements* on the use of alternate methods. This section also notes that in the event of a dispute, only the result obtained by the compendial test is conclusive.

Validation studies of alternate microbiological methods should take a large degree of variability into account. When conducting microbiological testing by conventional plate count, for example, one frequently encounters a range of results that is broader (%RSD 15 to 35) than ranges in commonly used chemical assays (%RSD 1 to 3). Many conventional microbiological methods are subject to sampling error, dilution error, plating error, incubation error, and operator error.

Validation of Compendial Methods ⟨1225⟩ defines characteristics such as accuracy, precision, specificity, detection limit, quantification limit, linearity, range, ruggedness, and robustness in their application to analytical methods. These definitions are less appropriate for alternate microbiological method validation as "at least equivalent to the compendial method" given the comparative nature of the question (see *Test and Assay—Procedures* section in *General Notices and Requirements*). The critical question is whether or not the alternate method will yield results equivalent to, or better than, the results generated by the conventional method.

Other industry organizations have provided guidance for the validation of alternate microbiological methods.[1] The suitability of a new or modified method should be demonstrated in a comparison study between the USP compendial method and the alternate method. The characteristics defined in this chapter may be used to establish this comparison.

~~Validation studies of microbiological methods must take into account a large degree of variability. When conducting microbiological testing by conventional plate count, for example, one frequently encounters a range of results that is broader than ranges in commonly used chemical assays. Many conventional microbiological methods are subject to sampling error, dilution error, plating error, and operator error.~~

~~*Validation of Compendial Methods* ⟨1225⟩ defines characteristics such as accuracy, precision, specificity, detection limit, quantification limit, linearity, range, ruggedness, and robustness in their application to chemical and physical testing. These definitions are not appropriate for microbiological method validation as "at least equivalent to the compendial method" because of the comparative nature of the question. For example, while the concept of "detection limit" has merit in quantitative microbial assays, the critical question is whether the alternate method will yield data equal to, or of higher quality than, the data generated by the conventional method.~~

~~The value of a new or modified method should be demonstrated in a comparison study between the USP compendial method and the alternate method. The characteristics defined in this chapter should be used to establish this comparison.~~

TYPES OF MICROBIOLOGICAL TESTS

It is critical to the validation effort to identify the portion of the test addressed by that alternate technology. For example, there is a variety of technologies available to detect the presence of viable cells. These techniques may have application in a variety of tests (e.g., bioburden, sterility test) but

[1] PDA Technical Report No. 33. The Evaluation, Validation and Implementation of New Microbiological Testing Methods. *PDA Journal of Pharmaceutical Science & Technology.* 54 Supplement TR#33 (3) 2000 and Official Methods Programs of AOAC International.

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may not, in fact, replace the critical aspects of the test entirely. For example, a sterility test by membrane filtration may be performed according to the compendial procedure up to the point of combining the processed filter with the recovery media, and after that the presence of viable cells might then be demonstrated by use of some of the available technologies ~~(see *Table 1*)~~. Validation of this application would, therefore, require validation of the recovery system employed rather than the entire test.

~~**Table 1. Examples of Technologies to Demonstrate the Presence of Viable Organisms**~~

~~Technology~~	~~Application~~
~~growth in liquid culture~~	~~qualitative determination~~
~~impedance~~	~~qualitative determination~~
~~ATP bioluminescence~~	~~qualitative determination~~
~~flow cytometry~~	~~qualitative determination~~
~~head space gas measurement~~	~~qualitative determination~~
~~plate counts~~	~~quantitative determination~~
~~epifluorescent vital dye~~	~~quantitative determination~~

There are three major types of determinations specific to microbiological tests. These include tests to determine whether microorganisms are present in a sample, tests to quantify the number of microorganisms (or to enumerate a specific subpopulation of the sample), and tests designed to identify microorganisms. This chapter does not address microbial identification.

Qualitative Tests for the Presence or Absence of Microorganisms

~~The sterility test is the most common example of this test; the turbidity of a liquid growth medium is taken as evidence of the presence of viable microorganisms in the test sample.~~ This type of test is characterized by the use of turbidity in a liquid growth medium as evidence of the presence of viable microorganisms in the test sample. The most common example of this test is the sterility test. Other examples of this type of testing are those tests designed to evaluate the presence or absence of a particular type of microorganism in a sample (e.g., coliforms in potable water, ~~*Listeria monocytogenes* in food,~~ *E. coli* in oral dosage forms, etc.).

Quantitative Tests for ~~Enumeration of~~ Microorganisms

~~The standard plate count method is the archetype of this class of tests used to estimate the number of viable microorganisms present in a sample. The Most Probable Number (MPN) method is another of these tests. MPN was developed as a means to estimate the number of viable microorganisms present in a sample not amenable to direct plating.~~ The plate count method is the most common example of this class of tests used to estimate the number of viable microorganisms present in a sample. The membrane filtration and Most Probable Number (MPN) multiple-tube methods are other examples of these tests. The latter was developed as a means to estimate the number of viable microorganisms present in a sample not amenable to direct plating or membrane filtration.

~~Identification Tests~~

~~The classical methods of identification used in compendial tests are biochemical and morphological characterization of an unknown microorganism. Biochemical and morphological characterization of an unknown microorganism is the classical method of identification used in compendial tests. Recently developed methods have streamlined and automated aspects of this identification test, especially in the areas of data handling, analysis, and storage. Several~~

~~new approaches that have been integrated into these methods include biochemical reactions, carbon substrate utilization, characterization of fatty acid composition, and restriction endonuclease banding patterns of 16S rDNA.~~

General Concerns

~~Validation of a microbiological method is the process by which it is experimentally established that the performance characteristics of the method meet the requirements for the intended application. Since microbiological tests have three basic applications, three separate sets of validation criteria are required. These concerns are described below, and summarized in *Table 2*.~~

~~Table 2. Validation Parameters by Type of Microbiological Test~~

~~Parameter~~	~~Qualitative Tests~~	~~Quantitative Tests~~	~~Identification Tests~~
~~accuracy~~	~~yes~~	~~yes~~	~~yes~~
~~precision~~	~~no~~	~~yes~~	~~no~~
~~specificity~~	~~yes~~	~~yes~~	~~yes~~
~~detection limit~~	~~yes~~	~~yes~~	~~no~~
~~quantification limit~~	~~no~~	~~yes~~	~~no~~
~~linearity~~	~~no~~	~~yes~~	~~no~~
~~range~~	~~no~~	~~yes~~	~~no~~
~~robustness~~	~~yes~~	~~yes~~	~~yes~~
~~ruggedness~~	~~yes~~	~~yes~~	~~yes~~

Validation of a microbiological method is the process by which it is experimentally established that the performance characteristics of the method meet the requirements for the intended application, in comparison to the traditional method. For example, it may not be necessary to fully validate the equivalence of a new quantitative method for use in the antimicrobial efficacy test by comparative studies, as the critical comparison is between the new method of enumeration and the plate count method (the current method for enumeration). As quantitative tests, by their nature, yield numerical data, they allow for the use of parametric statistical techniques. In contrast, qualitative microbial assays, e.g. the sterility test in the example above, may require analysis by nonparametric statistical methods. The validation of analytical methods for chemical assays follows well-established parameters as described in *Validation of Compendial Methods* ⟨1225⟩. Validation of microbiological methods share some of the same concerns, although consideration must be given to the unique nature of microbiological assays (see *Table 1*).

Table 1. Validation Parameters by Type of Microbiological Test

Parameter	Qualitative Tests	Quantitative Tests
Accuracy	No	Yes
Precision	No	Yes
Specificity	Yes	Yes
Detection limit	Yes	Yes
Quantification limit	No	Yes
Linearity	No	Yes
Operational range	No	Yes
Robustness	Yes	Yes
Repeatability	Yes	Yes
Ruggedness	Yes	Yes

In-Process Revision

VALIDATION OF QUALITATIVE TESTS FOR ~~RECOVERY OF MICROORGANISMS IN A SAMPLE~~ DEMONSTRATION OF VIABLE MICROORGANISMS IN A SAMPLE

~~Accuracy and Precision~~

~~*Definition*— The accuracy of a qualitative microbiological method is described as the closeness of the test results obtained by the test method to the value obtained by the compendial method.~~

~~*Determination*— An example of accuracy is shown in the case of a sterility test comparing the rate products produce positive and negative results using the alternative method versus the compendial method.~~

~~**Precision**—~~

~~*Definition*— The precision of a qualitative microbiological method is the degree of agreement between the alternate method and the compendial method when the procedures are performed repeatedly on different lots of the same product.~~

~~A direct method to show the equivalence of two qualitative assays would be to run them side by side and determine the degree to which the method under evaluation shows equivalence to the compendial method. An example of this could be the sterility test where this would translate into a comparison of the rate of positive and negative results produced by the alternative method versus the compendial method for identical samples. However, in a case such as the sterility test, the low number of failures would required thousands of comparison tests to establish equivalency and thus would be problematic.~~

~~A more feasible method for evaluating the precision of a qualitative microbiological method compared to a compendial method might be to observe the degree of agreement between the two when the procedures are performed repeatedly on different lots of the same product. The precision of an alternative qualitative microbiological method is may be expressed as the relative rates of false positive and false negative results between the new method and the compendial method using a standardized, low level inoculum.~~

~~*Determination*—~~

~~The rate of occurrence of false negative results in the presence of the sample for the two methods is can be estimated using low levels of standard challenge organisms. This design is similar to the standard bacteriostasis/fungistasis test; however, the level of microorganisms inoculated must be very low (not more than 5 cfu per unit). This low level of inoculum will ensure a frequency of failure rates high enough to provide a means to compare the two methods. The alternate method must provide at least as high a recovery as the compendial method.~~

Specificity

~~*Definition*—~~

The specificity of an alternate qualitative microbiological method is its ability to detect a range of microorganisms that may be present in the test article. This concern is adequately addressed by growth promotion of the media for qualitative methods that rely upon growth to demonstrate presence or absence of microorganisms. However, for those methods that do not require growth as an indicator of microbial presence, the specificity of the assay for microbes assures that extraneous matter in the test system does not interfere with the test.

~~*Determination*— This concern is adequately addressed by growth promotion of the media for qualitative methods that rely upon growth to demonstrate microbial presence or absence of microorganisms. However, for those methods that do not require growth as an indicator of microbial presence,~~

~~the specificity of the assay for microbes assures that extraneous matter in the test system does not interfere with the test.~~

~~Detection Limit~~ Limit of Detection

~~*Definition*~~

The limit of detection is the lowest number of microorganisms in a sample that can be detected under the stated experimental conditions. A microbiological ~~detection~~ limit test determines the presence or absence of microorganisms, e.g., absence of *Salmonella* spp. in 10 g. Due to the nature of microbiology, the limit of detection refers to the number of organisms present in the original sample before any dilution or incubation steps; it does not refer to the number of organisms present at the point of assay.

~~*Determination*~~

~~The two methods (alternative and compendial) are should be assessed by inoculation with a low number of standard challenge microorganisms (not more than 5 cfu per unit) followed by a measurement of recovery. The level of inoculation must should be adjusted until at least 50% of the samples show growth in the compendial test. It is necessary to repeat this determination several times, as the limit of detection of an assay is determined from a number of replicates (not less than 5). The ability of the two methods to detect the presence of single organisms can be demonstrated using the Chi square test.~~ One method to demonstrate the limit of detection for a quantitative assay would be to evaluate the two methods (alternative and compendial) by inoculation with a low number of challenge microorganisms (not more than 5 cfu per unit) followed by a measurement of recovery. The level of inoculation should be adjusted until at least 50% of the samples show growth in the compendial test. It is necessary to repeat this determination several times, as the limit of detection of an assay is determined from a number of replicates (not less than 5). The ability of the two methods to detect the presence of low numbers of microorganisms can be demonstrated using the Chi square test. A second method to demonstrate equivalence between the two quantitative methods could be through the use of the Most Probable Number technique. In this method, a 5-tube design in a ten-fold dilution series could be used for both methods. These would then be challenged with equivalent inoculums (for example, a 10^{-1}, 10^{-2}, and 10^{-3} dilution from a stock suspension of approximately 50 cfu per mL to yield target inocula of 5, 0.5, and 0.05 cfu per tube) and the MPN of the original stock determined by each method. If the 95% confidence intervals overlapped, then the methods would be considered equivalent.

~~**Quantification Limit, Linearity, and Range**~~ ~~Not applicable to qualitative assays.~~

Ruggedness

~~*Definition*~~

The ruggedness of a qualitative microbiological method is the degree of precision of test results obtained by analysis of the same samples under a variety of normal test conditions, such as different analysts, instruments, lots of reagents, laboratories, etc. Ruggedness can be defined as the intrinsic resistance to the influences exerted by operational and environmental variables on the results of the microbiological method. Ruggedness is a validation parameter best suited to determination by the supplier of the test method who has easy access to multiple instruments and batches of components.

~~*Determination*~~ ~~One method to demonstrate ruggedness is to prepare a suspension of microorganisms and test at least several replicates against each assay variable in order~~

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~~to compare values among laboratories. Attention must be paid to the inherent instability of microbiological suspensions, and experimental protocols must be randomized to eliminate bias. As there are no agreed upon standards for current methods, acceptance criteria are problematic. It is essential, however, that an estimate of the ruggedness of the alternate procedure be developed.~~

Robustness

~~*Definition*—~~

~~The robustness of a qualitative microbiological method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters, and provides an indication of the method's reliability during normal usage. Robustness is a validation parameter best suited to determination by the supplier of the test method. As there are no agreed upon standards for current methods, acceptance criteria are problematic and must be tailored to the specific technique. It is essential, however, that an estimate of the robustness of the alternate procedure be developed.~~ The robustness of a microbiological method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters, and provides an indication of its reliability during normal usage. Robustness is a validation parameter best suited to determination by the supplier of the test method. As there are no agreed upon standards for current methods, acceptance criteria are problematic and must be tailored to the specific technique. It is essential, however, that an estimate of the ruggedness of the alternate procedure be developed. The measure of robustness is not necessarily a comparison between the alternate method and the traditional, but rather a necessary component of validation of the alternate method so that the user knows the operating parameters of the method.

~~*Determination*—Robustness is a validation parameter best suited to determination by the supplier of the test method. As there are no agreed upon standards for current methods, acceptance criteria are problematic and must be tailored to the specific technique. It is essential, however, that an estimate of the robustness of the alternate procedure be developed.~~

VALIDATION OF QUANTITATIVE ESTIMATION OF VIABLE MICROORGANISMS IN A SAMPLE

As colony-forming units follow a Poisson distribution, the use of statistical tools appropriate to the Poisson rather than those used to analyze normal distributions is encouraged. If the user is more comfortable using tools geared towards normally distributed data, the use of a data transformation is frequently useful. Two techniques are available and convenient for microbiological data. Raw counts can be transformed to normally distributed data either by taking the $\log_{10}$ unit value for that count, or by taking the square root of count +1. The latter transformation is especially helpful if the data contain zero counts.

Accuracy

~~*Definition*—~~

~~The accuracy of a quantitative microbiological method is the closeness of the test results obtained by the alternate method to the value obtained by the compendial method. Accuracy must should be demonstrated across the practical range of the test. Accuracy is usually expressed as the percentage of recovery of microorganisms by the assay method.~~ The accuracy of this type of microbiological method is the closeness of the test results obtained by the alternate test method to the value obtained by the traditional method. It

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should be demonstrated across the operational range of the test. Accuracy is usually expressed as the percentage of recovery of microorganisms by the assay method.

~~*Determination* —~~

Accuracy ~~is demonstrated~~ in a quantitative microbiological test may be shown by preparing a suspension of microorganisms at the upper end of the range of the test, serially diluted down to the lower end of the range of the test. The operational range of the alternate method should overlap that of the traditional method. For example, if the alternate method is meant to replace the traditional plate count method for viable counts, then a reasonable range might be from 10^0 to 10^6 cfu per mL. ~~If it is, instead, a replacement for the MPN method, a much more narrow range may be used.~~ At least five suspensions across the range of the test ~~must~~ should be analyzed for each challenge organism. The alternate method ~~must~~ should provide an estimate of viable microorganisms not less than 70% of the estimate provided by the ~~compendial method.~~ traditional method, or the new method should be shown to recover at least as many organisms as the traditional method by appropriate statistical analysis. An example being an ANOVA analysis of the $\log_{10}$ unit transforms of the data points. Note that the possibility exists that an alternate method may recover an apparent higher number of microorganisms if it is not dependent on the growth of the microorganisms to form colonies or develop turbidity. This is determined in the *Specificity* evaluation.

Precision

~~*Definition* —~~

The precision of a quantitative microbiological method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of suspensions of laboratory microorganisms across the range of the test. The precision of a microbiological method is usually expressed as the standard deviation or relative standard deviation (coefficient of variation). However, other appropriate measures may be applied.

~~*Determination* —~~

~~Precision is demonstrated by preparing One method to demonstrate precision uses a suspension of microorganisms at the upper end of the range of the test that has been serially diluted down to the lower end of the range of the test. At least 5 suspensions across the range of the test must should be analyzed. For each suspension at least 10 replicates must should be assayed in order to allow for the calculation of statistically significant estimates of the standard deviation or relative standard deviation (coefficient of variation). Generally, a coefficient of variation in the 10% to 15% range is acceptable. Irrespective of the specific results, the alternate method must have a coefficient of variation that is not larger than that of the compendial method. Results ± 0.5 log are considered precise in microbiological testing.~~ One method to demonstrate precision uses a suspension of microorganisms at the upper end of the range of the test that has been serially diluted down to the lower end of the range of the test. At least 5 suspensions across the range of the test should be analyzed. For each suspension at least 10 replicates should be assayed in order to be able to calculate statistically significant estimates of the standard deviation or relative standard deviation (coefficient of variation). Generally, a RSD in the 15% to 35% range would be acceptable. Irrespective of the specific results, the alternate method should have a coefficient of variation that is not larger than that of the traditional method. For example, a plate count method might have the RSD ranges as shown in the following table.

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Table 2. Expected RSD as a Function of CFU per Plate

CFU per Plate	Expected RSD
30–300	< 15%
10–30	< 25%
< 10	< 35%

Specificity

~~*Definition*~~

~~The specificity of a quantitative microbiological method is its ability to detect a range of microorganisms that demonstrate that the method is fit for its intended purpose. This is demonstrated using the compendial organisms appropriate for the purpose of the alternate method.~~ The specificity of a microbiological method is its ability to detect a panel of microorganisms suitable to demonstrate that the method is fit for its intended purpose. This is demonstrated using the organisms appropriate for the purpose of the alternate method. It is important to challenge the alternate technology in a manner that would encourage false positive results (specific to that alternate technology) to demonstrate the suitability of the alternate method in comparison to the traditional method. This is especially important with those alternate methods that do not require growth for microbial enumeration (for example, any that do not require enrichment or can enumerate microorganisms into the range of 1–50 cells).

~~*Determination*~~ ~~Specificity is demonstrated using the compendial organisms.~~

~~**Detection Limit**~~ ~~Not applicable to quantitative assays.~~

~~Quantification Limit~~ Limit of Quantification

~~*Definition*~~

~~The limit of quantification is a parameter of quantitative assays for low levels of microorganisms in sample matrices.~~ It ~~is the lowest number of microorganisms that can be determined with acceptable precision and accuracy under the stated experimental conditions accurately counted. As it is not possible to obtain a reliable sample containing a known number of microorganisms, it is essential that the quantification limit of an assay is determined from a number of replicates ($n > 5$) at each of at least five different points across the range of the assay. The limit of quantification should not be a number greater than that of the compendial method.~~ The limit of quantification is the lowest number of microorganisms that can be accurately counted. As it is not possibleto obtain a reliable sample containing a known number of microorganisms, it is essential that the limit of quantification of an assay is determined from a number of replicates ($n > 5$) at each of at least five different points across the operational range of the assay. The limit of quantification should not be a number greater than that of the traditional method. Note that this may have an inherent limit due to the nature of bacterial enumeration and the Poisson distribution of bacterial counts (see *Validation of Microbial Recovery From Pharmacopeial Articles* ⟨1227⟩). Therefore, the alternate method need only demonstrate that it is at least as sensitive as the traditional method to similar lower limits.

~~*Determination*~~ ~~As it is not possible to obtain a reliable sample containing a known number of microorganisms, it is essential that the quantification limit of an assay is determined from a number of replicates ($n > 5$) at each of at least five different points across the range of the assay. The limit of quantification is not greater than the compendial method.~~

Linearity

~~*Definition*~~

The linearity of a quantitative microbiological test is its ability to produce results that are proportional to the concentration of microorganisms present in the sample within a

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given range. The linearity should be determined over the range of the test. A method to determine this would be to select at least five concentrations of each standard challenge microorganism and conduct at least five replicate readings of each concentration. ~~The appropriate measure of linearity is the F-test, demonstrating that deviations from linearity do not exceed the variability of the data. This is done by determining the ratios of deviations from the linearity mean square to the within-groups mean square. The F-ratio for the alternate method should not exceed that of the compendial test. The ratio of deviations from the linearity mean square to the within-groups mean square will equal 1 if the data are described by a straight line; if the data are not described by a straight line, this ratio will be greater than 1, as the deviations from linearity will exceed the variability of the data. The probability of the data variations can then be derived from a table of critical F values. Alternatively (or in addition), a graphic depiction of deviations from linearity can be plotted as residuals from the regression against the estimate. An unequal distribution of the residual values around zero would indicate nonlinearity. An alternate measure would be to calculate the correlation coefficient from a linear regression analysis of the data generated above.~~ An appropriate measure would be to calculate the square of the correlation coefficient, r^2, from a linear regression analysis of the data generated above. While the correlation coefficient does not provide an estimate of linearity, it is a convenient and commonly applied measure to approximate the relationship. The alternate method should not have an r^2 value less than 0.95.

~~*Determination*— The linearity must be determined over the range of the test. A method to determine this is to select at least five concentrations of each standard challenge microorganism and conduct at least five replicate readings of each concentration. The appropriate measure of linearity is the F-test, demonstrating that deviations from linearity do not exceed the variability of the data. This is done by determining the ratios of deviations from the linearity mean square to the within-groups mean square. The F-ratio for the alternate method not exceed that of the compendial test. The ratio of deviations from the linearity mean square to the within-groups mean square will equal 1 if the data are described by a straight line. This ratio will be greater than 1 if they are not a straight line, as the deviations from linearity will exceed the variability of the data. The probability of the data variations are derived from a table of critical F values. A graphic depiction of deviations from linearity can also be plotted as residuals from the regression against the estimate. An unequal distribution of the residual values around zero would indicate non-linearity.~~

Limit of Detection

See *Limit of Detection* under *Validation of Qualitative Tests for Demonstration of Viable Microorganisms in a Sample*.

Range

~~*Definition*—~~

~~The range of a quantitative microbiological method is the interval between the upper and lower levels of microorganisms that have been determined with precision, accuracy, and linearity using the method as written. The range of the method is demonstrated by verifying that the method provides acceptable precision, accuracy, and linearity when applied to samples throughout the range.~~ The operational range of a microbiological method is the interval between the upper and lower levels of microorganisms that have been demonstrated to be determined with precision, accuracy, and linearity.

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~~*Determination*—The range of the method is demonstrated by verifying that the method provides acceptable precision, accuracy, and linearity when applied to samples throughout the range.~~

Ruggedness

~~*Definition*—~~

~~The ruggedness of a quantitative microbiological method is the degree of precision of test results obtained by analysis of the same samples under a variety of normal test conditions, such as different analysts, instruments, lots of reagents, etc. Ruggedness is normally expressed as the lack of influence of operational and environmental variables of the microbiological method on test results. Ruggedness is a validation parameter best suited to determination by the supplier of the test method with easy access to multiple instruments and batches of components.~~ See *Ruggedness* under *Validation of Qualitative Tests for Demonstration of Viable Microorganisms in a Sample*.

~~*Determination*—Ruggedness is a validation parameter best suited to determination by the supplier of the test method with easy access to multiple instruments and batches of components.~~

Robustness

~~*Definition*—~~

~~The robustness of a microbiological method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness is a validation parameter best suited to determination by the supplier of the test method.~~

See *Robustness* under *Validation of Qualitative Tests for Demonstration of Viable Microorganisms in a Sample*.

~~*Determination*—Robustness is a validation parameter best suited to determination by the supplier of the test method.~~

~~VALIDATION OF ALTERNATIVE MICROBIAL IDENTIFICATION METHODS~~

~~There is a large body of evidence that different methods vary considerably in their ability to identify microorganisms in compendial articles. It must be accepted that a method of identification systematics needs to be internally consistent, but may differ from others in identification of unknown isolates. In other words, identification of an isolate based on biochemical activity may lead to one conclusion, identification by fatty acid analysis to another, identification by DNA analysis may lead to a third, and other methods may lead to alternate conclusions. Microbiological identifications by a particular system flow directly from previous experience with that system, and therefore may well differ from identifications by another system. It is critical that each system provide a consistent identification of isolates from compendial articles, but it is not required that each agree with all other methods.~~

~~Accuracy~~

~~*Definition*—~~

~~Not applicable beyond standard organisms. The accuracy of a microbiological identification method is the closeness of the test results obtained by the test alternative method to the value obtained by the compendial method. Accuracy should be demonstrated with a series of well-defined stock culture organisms.~~

~~*Determination*—Accuracy is demonstrated with a series of well-defined stock culture organisms.~~

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~~**Precision**~~

~~*Definition*—~~

~~The precision of a microbiological identification method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of suspensions of laboratory microorganisms across the range of the test.~~

~~**Specificity, Detection Limit, Quantification Limit, Linearity, and Range**—Not applicable to microbiological identification methods.~~

~~**Ruggedness**~~

~~*Definition*—~~

~~Ruggedness is normally expressed as the lack of influence of operational and environmental variables of the microbiological identification method on test results.~~

~~Ruggedness is normally expressed as the lack of influence on test results of operational and environmental variables of the microbiological method. Ruggedness is a validation parameter best suited to determination by the supplier of the test method with easy access to multiple instruments and batches of components.~~

~~*Determination*—Ruggedness is a validation parameter best suited to determination by the supplier of the test method with easy access to multiple instruments and batches of components.~~

~~**Robustness**~~

~~*Definition*—~~

~~The robustness of a microbiological method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters, robustness and provides an indication of its reliability during normal usage. Robustness is a validation parameter best suited to determination by the supplier of the test method, but in any event should not be less than that of the compendial method.~~

~~*Determination*—Robustness is a validation parameter best suited to determination by the supplier of the test method, but in any event does not exceed that of the compendial method.~~ ■2S (*USP29*)

BRIEFING

⟨**1230**⟩ **Water for Health Applications,** *USP 28* page 2754 and page 3333 of the *First Supplement.* It is proposed to revise the microbial culture media terminology in *Microbial Considerations* so that it conforms to that used in *Buffer Solution and Media* under *Microbial Limit Tests* ⟨61⟩.

(PW: F. Barletta) RTS—42974-1

Change to read:

MICROBIAL CONSIDERATIONS

The *Water for Hemodialysis* monograph includes microbial limits of 100 cfu per mL and endotoxin limits of 2 USP Endotoxin Units per mL. Culture media should be ~~tryptic soy agar~~

■Soybean–Casein Digest Agar Medium■2S (*USP29*) or equivalent, and colonies should be counted after incubation at a temperature range between 30° and 35°, for no less than 48 hours. Sampling the water should be done at the end of the water purification cascade at the point where the water enters the ■dialysis equipment. Samples should be assayed within 30 minutes of collection or immediately refrigerated and then assayed within 24 hours of collection.■1S (*USP28*) Quantification of bacterial endotoxins is performed using the Limulus Amebocyte Lysate (LAL) clotting method ■or any other LAL test■1S (*USP28*) found in the USP general test chapter *Bacterial Endotoxins Test* ⟨85⟩.

Because of the incubation time required to obtain definitive microbiological results, water systems should be microbiologically monitored to confirm that they continue to produce water of acceptable quality. Alert Levels and Action Levels are therefore necessary for the monitoring and control of the system. An Alert Level constitutes a warning and does not require a corrective action. An Action Level indicates a drift from normal operating conditions and requires that corrective action be taken ■to bring the process back into the normal operating range. Exceeding an Alert Level or Action Level does not imply that water quality has been compromised.■1S (*USP28*) The recommended Action Level for a total viable microbial count in the product water is 50 cfu per mL, and the recommended Alert Level for bacterial endotoxins is 0.5 USP Endotoxin Unit per mL (also see *Microbial Considerations* under *Water for Pharmaceutical Purposes* ⟨1231⟩).

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REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

2-Aminophenol, *USP 28* page 2798. It is proposed to update the information for this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—42681-2

Change to read:

2-Aminophenol

■(*o-aminophenol, 2-hydroxyaniline*),■2S (*USP29*)
C_6H_7NO—**109.13**

■[*95-55-6*]■2S (*USP29*)
—Off-white powder.

~~*Assay*—Inject an appropriate specimen into a 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 0.25 mm × 30 m capillary column coated with a 1 µm layer of phase G2; the injection port temperature is maintained at 230°; the detector temperature is maintained at 300°; and the column temperature is maintained at 130° and programmed to rise 10° per minute to 280°. The area of the C_6H_7NO peak is not less than 99% of the total peak area.~~

~~*Melting range* ⟨741⟩: between 174° and 177°.~~

■Use a suitable grade with a content of not less than 99%.■2S (*USP29*)

BRIEFING

3-Aminosalicylic Acid, *USP 28* page 2798. It is proposed to update the information for this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—42681-1

Change to read:

3-Aminosalicylic Acid, $C_7H_7NO_3$—**153.14**

■[*570-23-0*]■2S (*USP29*)
—Tan-grey powder.

~~*Assay*—When tested by thin-layer chromatography (see *Chromatography* ⟨621⟩) with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of a mixture of butanol, water, and acetic acid (60 : 25 : 15), examined under short-wavelength UV light, a single spot is exhibited, with trace impurities.~~

~~*Melting point* ⟨741⟩: 240°, with decomposition.~~

■Use a suitable grade with a content of not less than 97%.■2S (*USP29*)

BRIEFING

L-Arabinitol, *USP 28* page 2801. It is proposed to delete this reagent. It will become available as a USP Reference Standard.

(HDQ: M. Marques) RTS—42650-2

Delete the following:

■~~**L-Arabinitol,** (*L-Arabitol, 1,2,3,4,5-pentanepentol*), $C_5H_{12}O_5$—**152.15**—White crystals or crystalline powder. Stable in air. Freely soluble in water yielding a clear, colorless solution. Store in cool to room temperature in a dry area.~~

~~*Melting range* ⟨741⟩: between 102° and 104°.~~

~~*Water, Method I* ⟨921⟩: not more than 0.5%.~~

~~*Residue on ignition* ⟨281⟩: not more than 0.1%.~~■2S (*USP29*)

BRIEFING

Erythritol, *USP 28* page 2817. It is proposed to delete this reagent. It will become available as a USP Reference Standard.

(HDQ: M. Marques) RTS—42650-1

Delete the following:

■~~**Erythritol** (*Meso-erythritol, 1,2,3,4-butanetetrol*), $C_4H_{10}O_4$—**122.12**—Tetragonal prisms. Stable in air. Very soluble in water yielding a clear, colorless solution. Store in cool to room temperature in a dry area.~~

~~*Melting range* ⟨741⟩: between 118° and 120°.~~

~~*Water, Method I* ⟨921⟩: not more than 0.5%.~~

~~*Residue on ignition* ⟨281⟩: not more than 0.1%.~~■2S (*USP29*)

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BRIEFING

Galactitol, *USP 28* page 2820. It is proposed to delete this reagent. It will become available as a USP Reference Standard.

(HDQ: M. Marques) RTS—42650-3

Delete the following:

■~~**Galactitol** (*Dulcitol*), $C_6H_{14}O_6$ 182.17 White crystals or crystalline powder. Stable in air. One g dissolves in 30 mL of water to yield a clear, colorless solution. Store in cool to room temperature in a dry area.~~

~~*Melting range* ⟨741⟩: between 188° and 189°.~~

~~*Water, Method I* ⟨921⟩: not more than 0.5%.~~

~~*Residue on ignition* ⟨281⟩: not more than 0.1%.~~ ■2S (*USP29*)

BRIEFING

Lead Standard Solution. This new reagent is used to prepare the *Standard lead solution* in the test for *Limit of lead* under *Calcium Silicate,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41797-2

Add the following:

■**Lead Standard Solution**—A solution containing $Pb(NO_3)_2$ in 0.5 M Nitric acid corresponding to 1000 mg of lead/mL.

[NOTE—A suitable grade is available as catalog number 1.19776 from EMD Chemicals, www.emdchemicals.com.]■2S (*USP29*)

BRIEFING

Magnesium Matrix Modifier. This new reagent is used to prepare the *Matrix modifier solution* in the test for *Limit of lead* under *Calcium Silicate,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41797-2

Add the following:

■**Magnesium Matrix Modifier**—Magnesium Nitrate (2% MG).

[NOTE—Available as catalog number RCMMMG20KN-50, from VWR, www.vwr.com.]■2S (*USP29*)

BRIEFING

Nitric Acid, 65 Percent. This new reagent is used to prepare the *Nitric acid diluent* in the test for *Limit of lead* under *Calcium Silicate,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41797-2

Add the following:

■**Nitric Acid, 65 Percent**—[*7697-37-2*]—Use a suitable grade with a content of not less than 65.0%.

[NOTE—A suitable grade is available as catalog number 441-2 from EMD Chemicals, www.emdchemicals.com.]■2S (*USP29*)

BRIEFING

Palladium Matrix Modifier. This new reagent is used to prepare the *Matrix modifier solution* in the test for *Limit of lead* under *Calcium Silicate,* which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—41797-2

Add the following:

■**Palladium Matrix Modifier**—Palladium Nitrate (1% PD).

[NOTE—A suitable grade is available as catalog number RCMMPD10KN-50 from VWR, www.vwr.com.]■2S (*USP29*)

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Test Solutions

BRIEFING

Test Solutions, *USP 28* page 2855, page 3338 of the *First Supplement,* and page 859 of *PF* 31(3) [May–June 2005]. It is proposed to correct the procedure used in the preparation of Sodium Tetraphenylboron TS.

(HDQ: M. Marques) RTS—42679-1

Add the following:

■**Phenol TS**—Dissolve 1.2 g of phenol in alcohol to make 10 mL. Prepare weekly.■1S (*USP29*)

Add the following:

■**Sodium Citrate TS, Alkaline**—Dissolve 50 g of sodium citrate dihydrate and 2.5 g of sodium hydroxide in water to make 250 mL.■1S (*USP29*)

Change to read:

Sodium Tetraphenylboron TS—Dissolve 1.2 g of sodium tetraphenylboron in water to make 200 mL. If necessary, stir for 5 minutes with 1 g of ~~freshly prepared hydrous~~

■■2S (*USP29*)
aluminum oxide, and filter to clarify.

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 28* page 2862, page 3630 of the *Second Supplement,* and page 108 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to revise the formula for calculation of the normality of 0.01 N Iodine VS. It is also proposed to change the 50% (w/w) sodium hydroxide solution used to prepare 0.1 N Alcoholic Sodium Hydroxide VS to a 50% (w/v) solution.

(HDQ: M. Marques) RTS—42675-1; 42676-1

Change to read:

Iodine, Hundredth-Normal (0.01 N)
I, **126.90**

1.269 g in 1000 mL

Dissolve about 1.4 g of iodine in a solution of 3.6 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL, and standardize the solution as follows.

Transfer 100.0 mL of iodine solution to a 250-mL flask, add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS, and continue titrating until the solution is colorless. ■■1S (*USP28*)

Preserve in amber-colored, glass-stoppered bottles.

~~■$N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{25}$■1S (*USP28*)~~

■$N = \frac{\text{mL } Na_2S_2O_3 \times \text{N } Na_2S_2O_3}{100}$■2S (*USP29*)

Add the following:

▲**Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol**
CH_3OLi, **37.97**

3.798 g in 1000 mL

Dissolve 500 mg of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of methanol. If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under *Sodium Methoxide, Tenth-Normal (0.1 N) in Toluene*.

NOTE—Restandardize the solution frequently.

$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL lithium methoxide (corrected for the blank)}}$ ▲*USP29*

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Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)
NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% ~~(w/w)~~ ■(w/v)■2S (*USP29*) solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced.

$$\text{■N} = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}}\ \text{■1S (}USP28\text{)}$$

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869, page 3639 of the *Second Supplement,* and page 1191 of *PF* 31(4) [July–Aug. 2005].

(HDQ) RTS—39091-2; 39091-3; 39383-1; 41465-1; 42596-2

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:	
■Benazepril Tablets	W■1S (*USP29*)
Add the following:	
■Citalopram ~~Hydrobromide~~ Tablets	W■1S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Black Cohosh Tablets	T, LR■1S (*USP29*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W■1S (*USP29*)
Add the following:	
■Diclofenac Potassium Tablets	T, LR■2S (*USP29*)
Add the following:	
■Didanosine Tablets	T■2S (*USP29*)
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W■1S (*USP29*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W■1S (*USP29*)
Add the following:	
■Fosinopril Sodium Tablets	T■1S (*USP29*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T■1S (*USP29*)
Add the following:	
■Ginkgo Capsules	T, LR■1S (*USP29*)
Add the following:	
■Ginkgo Tablets	T, LR■1S (*USP29*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■■1S (*USP29*)
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR■1S (*USP29*)

In-Process Revision

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Irbesartan Tablets	$W_{■1S\ (USP29)}$
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	$W_{■1S\ (USP29)}$
Add the following:	
■Isosorbide Mononitrate Tablets	$T_{■1S\ (USP29)}$
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	$T_{■1S\ (USP29)}$
Add the following:	
■Ketoprofen Capsules, Extended-Release	$T_{■2S\ (USP29)}$
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	$W, LR_{■1S\ (USP29)}$
Add the following:	
▲Methscopolamine Bromide Tablets	$T_{▲USP29}$
Add the following:	
■Modafinil Tablets	$T_{■1S\ (USP29)}$
Add the following:	
■Nefazodone Hydrochloride Tablets	$T_{■2S\ (USP29)}$
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	$W_{■1S\ (USP29)}$
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	$T, LR_{■2S\ (USP29)}$

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Quinapril Tablets	$W_{■1S\ (USP29)}$
Add the following:	
■Tizanidine Tablets	$T_{■1S\ (USP29)}$
Add the following:	
Valerian Capsules	$T, LR_{■1S\ (USP29)}$
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	$W_{■1S\ (USP29)}$
Add the following:	
▲Zinc Sulfate Tablets	$W_{▲USP29}$

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 3640 of the *Second Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], and page 1193 of *PF* 31(4) [July–Aug. 2005].

(HDQ) RTS—36919-1; 41977-1; 42281-1; 42281-2; 42596-1; 42709-1; 42741-1; 42813-1

Add the following:

■**Didanosine:** White to off-white, crystalline powder. Very soluble in dimethyl sulfoxide; practically insoluble or insoluble in acetone and in methanol.■2S *(USP29)*

In-Process Revision

Add the following:

■**Divalproex Sodium:** White to off-white powder. Very soluble in chloroform; freely soluble in methanol and in ethyl ether; soluble in acetone; practically insoluble in acetonitrile.■2S (*USP29*)

Add the following:

■**Erythritol:** White or almost white, crystalline powder or free-flowing granules. It is stable to heat and is nonhygroscopic. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Humectant; sweetening agent.■2S (*NF24*)

Add the following:

■**Leflunomide:** White to almost white powder. Freely soluble in methanol, in alcohol, in 2-propanol, in ethyl acetate, in acetone, in acetonitrile, and in chloroform; practically insoluble in water.■2S (*USP29*)

Add the following:

■**Potassium Alginate:** White to yellow, fibrous or granular powder. Dissolves in water to form a viscous, colloidal solution; insoluble in alcohol and in hydroalcoholic solutions in which alcohol content is greater than 30% by weight; insoluble in chloroform, in ether, and in acids having a pH lower than about 3.■2S (*NF24*)

Add the following:

■**Pravastatin Sodium:** White to yellowish white, hygroscopic powder. Freely soluble in water and in methanol; soluble in alcohol; very slightly soluble in acetonitrile; practically insoluble in ether, in ethyl acetate, and in chloroform.■2S (*USP29*)

Add the following:

■**Prednicarbate:** White to almost white, crystalline powder. Freely soluble in acetone and in alcohol; sparingly soluble in propylene glycol; practically insoluble in water.■2S (*USP29*)

Add the following:

■**Tylosin Tartrate:** Almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids.■2S (*USP29*)

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 31(1) through 31(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF*.

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
General Notices—*Tests and Assays—Foreign Substances and Impurities; Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs* (*Controlled Cold Temperature*-added)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Oral Suspension—*USP Reference standards [USP4-Aminophenol RS]* (add), *Limit of 4-aminophenol* (add)	30	5	1579
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophenand Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets— *Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Acyclovir—*Assay and limit for guanine*	30	5	1580
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Albumin Human—*Definition, Expiration date, USP Reference standards,* (add), *Identification A, B* (add), *pH* (add), *Molecular size distribution* (add), *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add), *Packaging and storage, Labeling, Bacterial endotoxins* (add), *Sterility* (add), *Heat sterility* (add), *Safety* (add)	29	4	992
Albuterol Tablets—*Dissolution, Assay*	31	3	726
Allopurinol—*USP Reference standards, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (namechange)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Amphetamine Sulfate—*Assay*	31	2	381
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin Boluses—*Dissolution*	31	4	1026
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Tablets—*Dissolution*	30	1	61
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	29	3	606
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Betamethasone Tablets—*Dissolution*	30	1	62
Betamethasone Acetate—*Identification B*	31	2	381
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Budesonide (new)	30	6	1978
Bupropion Hydrochloride—*Chromatographic purity*	31	2	381
Bupropion Hydrochloride Extended-Release Tablets—*USP Reference standards, Related compounds*	31	2	384
Buspirone Hydrochloride—*Content of chloride*	31	3	742

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcitonin Salmon (new)	31	4	1036
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	29	5	1433
Calcitriol Injection (new)	29	5	1434
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Camphor—*Water*	31	3	742
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium Suspension (new)	30	3	812
Cefaclor Tablets (new)	29	6	1858
Cefadroxil for Oral Suspension—*Water*	31	4	1045
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Ciprofloxacin—*USP Reference standards, Other requirements*	31	2	393
Ciprofloxacin Injection—*Definition, USP Reference standards, Pyrogen* (delete), *Bacterial endotoxins* (add)	31	2	393
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	4	1046
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid*	31	2	394
Cladribine (new)	31	2	395
Clotrimazole Lozenges—*Disintegration* (delete), *Dissolution* (add)	31	2	398
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Dibucaine—*Identification B*	31	2	399
Dibucaine Cream—*Identification, Assay*	31	2	399
Dibucaine Ointment—*Identification*	31	2	400
Dibucaine Hydrochloride—*Labeling* (add), *USP Reference standards, Identification B, Other requirements* (add)	31	2	400
Dibucaine Hydrochloride Injection—*Identification A*	31	2	401
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add), *Assay*	29	6	1870
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dorzolamide Hydrochloride—*Limit of dorzolamide hydrochloride related compound A, Assay*	31	2	401
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Drospirenone (new)	31	3	754
Dyclonine Hydrochloride—*Identification B*	31	1	42
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Epinephrine Injection—*Identification A, B*	31	1	43
Estradiol and Norethindrone Acetate Tablets (new)	30	6	1989
Estradiol Transdermal System (new)	31	4	1063
Conjugated Estrogens—*Definition*	30	3	840
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add),*Related compounds*	31	4	1067
Ethosuximide Capsules—*Dissolution*	30	1	102
Etodolac Extended-Release Tablets—*Labeling* (add), *Dissolution*	31	4	1068
Fenofibrate (new)	31	3	763
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine HydrochlorideExtended-Release Tablets (new)	31	2	403
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Related compounds*	31	2	408
Fluoxetine Delayed-Release Capsules (new)	30	3	849
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propianate—*Chemical information, Definition, Content of acetone, Assay*	31	4	1070
Fluticasone Propianate Nasal Spray (new)	31	4	1071
Fluvastatin Capsules (new)	31	1	47
Fluvastatin Sodium (new)	31	1	43
Fluvoxamine Maleate Tablets (new)	30	5	1622
Fosinopril Sodium (new)	30	6	2001
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Gabapentin Capsules (new)	28	7	298
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification, Dissolution*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	2	410
Guaifenesin Capsules—*Dissolution*	30	1	106

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Guaifenesin Tablets—*Dissolution*	30	1	107
Helium—*USP Reference standards* and *Assay* (postponed indefinitely)	31	4	1014
Helium—*Definition, Packaging and storage*	31	4	1077
Hydrocodone Bitartrate—*USP Reference standards [USP Hydrocodone Bitartrate Related Compound A RS], Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Indocyanine Green—*Definition, Assay*	29	6	1905
Iodixanol—*Labeling* (add), *USP Reference standards, Limit of calcium, Other requirements* (add)	31	1	54
Irbesartan Tablets (new)	31	4	1080
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
Diluted Isosorbide Mononitrate—*pH*	31	4	1060
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Ketoprofen—*Assay*	31	3	772
Leuprolide Acetate (new)	30	3	882
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lidocaine Hydrochloride—*Assay*	31	2	415
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	31	2	415
Lipid Injectable Emulsion (new)	31	2	416
Lisinopril Tablets—*Dissolution*	31	4	1090
Loratadine Oral Solution—*Antimicrobial effectiveness test* (delete)	31	1	56
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	26	4	1050
Magnesium Chloride—*Identification, Insoluble matter*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mannitol Injection—*Labeling*	28	1	73
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Mefloquine Hydrochloride—*Related compounds*	31	4	1091
Meloxicam (new)	31	1	57
Meperidine Hydrochloride—*Packaging and storage, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	62
Meprobamate Tablets—*Dissolution*	30	1	129
Mesalamine—*Related compounds*	31	2	424
Metformin Hydrochloride—*Packaging and storage* (add), *Related compounds*	31	4	1092

Pending Proposals (*continued*)
(Items from earlier numbers of PF that have not yet been adopted and become official)

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Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methenamine Tablets—*Dissolution*	30	1	130
Methenamine Hippurate Tablets—*Labeling* (add), *Dissolution*	31	1	63
Methocarbamol Tablets—*Dissolution*	30	1	130
Methscopolamine Bromide (new)	31	2	425
Methscopolamine Bromide Tablets (new)	31	2	427
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Nabumetone—*Related compounds*	31	1	63
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nalidixic Acid—*Assay*	30	1	132
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage*	30	4	1264
Nefazodone Hydrochloride (new)	31	4	1094
Nefazodone Hydrochloride Tablets (new)	31	4	1096
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Nitrous Oxide—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1014
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100
Ondansetron Oral Solution—*Packaging and storage*	30	3	905
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete),*Related compounds* (add), *Assay*	31	1	64
Oxandrolone Tablets—*Labeling* (add), *Dissolution*	31	3	781
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new)	30	4	1276
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Paroxetine Tablets—*Identification A, C*	31	2	435
Paroxetine Hydrochloride—*USP Reference standards, Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine, Chromatographic purity*	31	4	1112
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	72

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Pentobarbital Sodium—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Bromide (new)	31	2	441
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Quinapril Tablets—*Packaging and storage*	29	4	1071
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards [USP Ranitidine Resolution Mixture RS], Chromatographic purity, Assay*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	30	6	2036
Oral Rehydration Salts—*USP Reference standards* (add), *Assay for citrate*	31	2	445
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Ritonavir (new)	31	3	788
Saccharin Calcium (new)—*Harmonization*	31	2	607
Saccharin Sodium (new)—*Harmonization*	31	4	1225
Scopolamine Hydrobromide—*Identification A*	31	1	73
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bromide (new)	31	2	446
Sodium Chloride—*Identification, Loss on drying, Limit of potassium*	31	3	795
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797

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Sodium Polystyrene Sulfonate Suspension—*Definition, Labeling* (delete), *USP Reference standards* (delete), *Assay for sorbitol* (delete)	31	4	1115
Sodium Salicylate Tablets—*USP Reference standards* (add)	31	4	1116
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone Oral Suspension (new)	30	3	929
Spironolactone Tablets—*Assay*	31	1	74
Spironolactone and Hydrochlorothiazide Oral Suspension (new)	30	3	930
Succinylcholine Chloride—*Chromatographic purity*	31	1	74
Sulfamethazine Granulated—*Assay*	31	3	797
Tazobactam (new)	31	4	1116
Technetium 99Tc Fanolesomab Injection (new)	31	2	448
Terbutaline Sulfate—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	75
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Terbutaline Sulfate Tablets—*USP Reference standards, Dissolution*	31	1	76
Tetracaine Hydrochloride—*Identification A*	31	2	451
Thalidomide—*Chromatographic purity*	31	2	452
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Thioridazine Hydrochloride—*Identification*	31	3	798
Tiagabine Hydrochloride—*Chromatographic purity*	30	5	1649
Tiamulin (new)	31	1	77
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Titanium Dioxide (NL to come)—*New Monograph [UV Attenuation]*	30	4	1304
Tizanidine Tablets (new)	31	2	456
Tizanidine Hydrochloride (new)	31	2	452
Tolazamide—*Chromatographic purity*	31	4	1118
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	31	4	1119
Travoprost Ophthalmic Solution (new)	31	4	1121
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay forcitrate*	31	2	465
Triclosan—*USP Reference standards, Limit of monochlorophenols and 2,4-dichlorophenol, Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran*	30	6	2054
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Ursodiol Capsules—*Dissolution*	31	3	800
Valsartan (new)	29	6	1996
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valpoic Acid Injection (new)	31	3	801
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127

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Purified Water—*Definition*	31	2	467
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins, Oxidizable substances*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Zinc Oxide—*Iron and other heavy metals*	31	1	80
Zinc Oxide Neutral (new)	31	1	80
Zinc Sulfate Oral Solution (new)	31	2	468
Zinc Sulfate Tablets (new)	31	1	82
<u>*Dietary Supplements Monographs*</u>			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Choline Chloride—*Limit of total amines*	31	1	84
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Powdered Ginkgo Extract (new)	27	2	2233
Ginkgo Capsules (new)	27	2	2238
Ginkgo Tablets (new)	27	2	2240
American Ginseng Capsules (new)	30	2	565
American Ginseng Tablets—*Dissolution [to come]*	30	2	567
Asian Ginseng Capsules (new)	30	2	571
Lutein—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1133
Lutein Preparation—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1134
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Psyllium Husk—*Definition, Light extraneous matter, Heavy extraneous matter* (delete)	30	6	2077
Pygeum Extract—*Packaging and storage*	30	3	956

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Selenomethionine—*USP Reference standards, Assay*	31	2	482
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian Capsules (new)	27	1	1825
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Foreign and Particulate Matter*	31	4	1149
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192
⟨11⟩ USP Reference Standards—	26	4	1101
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	5	1468
	29	3	710
	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
⟨41⟩ Weights and Balances—*Introduction, Weights, Balances*	31	2	508
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, GeneralProcedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Proce dures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨341⟩ Antimicrobial Agents—Contents—*General Gas Chromatographic Method, Polarographic Method*	30	5	1678
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨386⟩ Environmentally Sensitive Preparations (new)	30	5	1680
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909

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⟨621⟩ Chromatography—*Interpretation of Chromatograms, System Suitability, Glossary of Symbols,*	31	3	825
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨711⟩ *Dissolution Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain-Coated Tablets* (delete)	30	1	234
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	30	6	2235
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨841⟩ Specific Gravity—*Introduction, Method I, Method II* (add)	31	2	515
⟨851⟩ Spectrophotometry and Light-Scattering—*Procedure*	30	5	1703
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new)	31	4	1157
⟨1065⟩ Ion Chromatography (new)	31	2	519
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1075⟩ Good Compounding Practices—*Introduction, Applicable Definitions, Responsibilities of the Compounder, Training, Procedures and Documentation, Drug Compounding Facilities, Drug Compounding Equipment, Component Selection Requirements, Packaging and Drug Product Containers, Compounding Controls, Labeling, Records and Reports, Compounding for a Prescriber's Office Use, Compounding Veterinarian Products, Compounding Pharmacy Generated Products* (delete)	31	1	101
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceuti cal Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709

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⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1119⟩ Near-Infrared Spectrophotometry—*Instrumentation*	30	6	2137
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)	31	4	1180
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	29	1	256
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1232⟩ Instrumentation for Analysis of High Purity PharmaceuticalWaters (new)	30	5	1806
⟨2023⟩ Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements—*Supplement Components, Microbiological Testing*	30	5	1818
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
<u>*Reagent Specifications*</u>			
Acetanilide	31	2	572
Acetyl Chloride	31	2	573
Acetylcholine Chloride	31	2	573
4-Amino-6-chloro-1,3-benzenedisulfonamide	31	2	573

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3-Aminopropionic Acid	31	4	1189
Amyl Acetate	31	2	574
tert-Amyl Alcohol	31	2	574
Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form	31	3	858
L-Asparagine	31	2	574
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (add)	29	1	265
Benzaldehyde	31	2	574
Benzphetamine Hydrochloride	31	2	575
Benzyltrimethylammonium Chloride	31	2	575
Biphenyl	31	2	575
N-Bromosuccinimide	31	2	575
1-Butaneboronic Acid (delete)	31	4	1189
2,3-Butanedione	31	2	576
n-Butyl Chloride	31	2	576
Butyl Methacrylate (add)	31	4	1189
n-Butylboronic Acid	31	4	1189
Cadmium Acetate	31	2	576
Calcium Citrate	31	2	577
Calcium Lactate	31	2	577
Casein	31	2	578
Charcoal, Activated	31	2	578
Chlorobenzene	31	2	578
Congo Red	31	2	578
Cyclohexanol	31	2	579
Deuterated Methanol (new)	29	6	2054
o-Dichlorobenzene	31	2	579
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl	31	3	858
Dicyclohexylamine	31	2	579
Diidofluorescein	31	2	579
DEAE-Agarose (add)	29	1	265
1,2-Dimethoxyethane	31	2	580
2-Dimethylaminoethyl Methacrylate (add)	31	4	1190
N,N-Dimethyldodecylamine-*N*-oxide (add)	27	4	2837
Docusate Sodium (add)	31	4	1190
Dodecyltrimethylammonium Bromide (new)	31	3	859
Ethyl Cyanoacetate	31	2	580
Ethylene Glycol	31	2	580
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
Ferric Ammonium Citrate	31	2	581
Furfural	31	4	1190
Guaiacol	31	2	581
n-Heptane, Chromatographic	31	2	581
Hexadimethrine Bromide (add)	29	1	265
Hexamethyldisilazane	31	2	581
Hexane, Solvent	31	2	582
Inositol	31	2	582
Isoferulic Acid (add)	27	4	2837
Isopropylamine	31	2	582
Maleic Acid	31	2	583
Methyl Acetate	31	2	583
Methyl Red (add)	31	1	108
1-Naphthol	31	2	583
2-Naphthol	31	2	583
5-Nitro-1,10-phenanthroline	31	2	584
Nonylphenoxypoly(ethyleneoxy)ethanol	31	2	584
Para-aminobenzoic Acid	31	2	584
Paraformaldehyde	31	2	584
Propionic Anhydride	31	2	585

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Pyrrole	31	2	585
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Rose Bengal Sodium	31	2	585
Thrombin Human (new)	29	6	2055
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
Silver Oxide	31	2	585
Sodium Arsenite	31	2	586
Sodium Chromate	31	2	586
Sodium Glycocholate	31	2	587
Sodium 1-Hexanesulfonate Monohydrate (new)	31	2	587
Tetramethylammonium Hydroxide	31	2	587
Thioglycolic Acid	31	4	1190
Thymol	31	2	588
n-Tricosane	31	2	588
Triethylamine	31	2	588
2,4,6-Trimethylpyridine	31	2	588
1-Vinyl-2-pyrrolidone	31	1	108
Zinc Sulfate Heptahydrate (add)	26	2	504
Test Solutions			
Phenol TS (new)	31	3	859
Sodium Citrate TS, Alkaline (new)	31	3	859
Volumetric Solutions			
Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol	31	1	112
Reference Tables			
Container Specifications for Capsules and Tablets	31	4	1191
Excipients, USP and NF Excipients, Listed by Category	31	4	1128
Description and Solubility	25	4	8589
	25	6	9254
	26	4	1135
	27	1	1908
	28	2	554
	28	6	1953
	29	1	266
	29	4	1262
	29	5	1684
	30	4	1405
	30	5	1822
	31	1	122
	31	2	591
	31	3	861
	31	4	1193
NF Monographs			
Acesulfame Potassium—*Packaging and storage* (add)	31	1	87
Adipic Acid—*Packaging and storage* (add), *USP Reference standards* (add)	31	1	87
Alfadex—*Packaging and storage*	30	1	202
Amino Methacrylate Copolymer (new)	31	4	1137
Ammonio Methacrylate Copolymer Dispersion—*Identification A, B*	31	2	483
Asparagine—*Packaging and storage* (add), *USP Reference standards, Identification, Chromatographic purity*	31	1	87
Purified Bentonite—*Assay for aluminum and magnesium content*	31	2	483
Butylparaben (new)—*Harmonization*	31	1	191

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Calcium Silicate—*Definition, pH, Limit of fluoride, Assay of silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	30	2	595
Carbomer 934—*Labeling*	31	2	484
Carbomer 934 P—*Labeling* (add), *Limit of benzene*	31	2	484
Carbomer 940—*Labeling, Viscosity*	31	2	485
Carbomer 941—*Labeling*	31	2	485
Carbomer 1342—*Labeling*	31	2	485
Carbomer Copolymer—*Definition, Labeling, Limit of benzene* (add), *Organic volatile impurities* (add), *Content of carboxylic acid*	31	2	486
Carbomer Homopolymer (new)	31	2	488
Carbomer Interpolymer—*Labeling, Limit of benzene* (add), *Organic volatile impurities* (add)	31	2	493
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity*	31	4	1139
Microcrystalline Cellulose—*Labeling, Particle size distribution*	31	4	1139
Cetostearyl Alcohol—*Assay*	31	2	494
Cetyl Alcohol—*Assay*	31	2	494
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Crospovidone—*Monograph*	28	4	1257
Cyclomethicone—*Identification*	31	4	1140
Dibutyl Sebacate—*Saponification value*	31	4	1140
Diisopropanolamine (new)	31	4	1140
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Galactose—*Packaging and storage* (add)	31	1	88
Glyceryl Monostearate—*USP Reference standards* (delete), *Hydroxyl value, Saponification value, Assay for monoglycerides*	31	2	495
Purified Honey (new)	31	2	496
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isomalt (new)	31	1	88
Lactitol—*Related compounds*	31	4	1143
Lauroyl Macrogoglycerides (new)	28	4	1212
Lauroyl Polyoxylglycerides (new)	31	1	92
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate—*Harmonization*	30	1	340
Maltitol (new)	31	4	1143
Methacrylic Acid Copolymer—*Limit of monomers*	31	1	93
Neotame (new)	31	2	497
Nitrogen—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1015
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent —*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1015
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Phenolsulfonphthalein—*Labeling* (add), *USP Reference standards* (add), *Bacterial endotoxins* (add)	31	1	94
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Organic volatile impurities*	31	1	95
Propylene Glycol Dilaurate (new)	31	2	500
Propylene Glycol Monolaurate (new)	31	2	501
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618
Sesame Oil—*USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233

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Sodium Caprylate—*Packaging and storage*	30	3	990
Sodium Starch Glycolate—*Harmonization*	30	4	1455
Sodium Sulfite—*Identification*	31	4	1146
Sodium Tartrate—*Packaging and storage*	31	1	95
Rice Starch (new)—*Harmonization*	30	2	721
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Succinic Acid—*Packaging and storage*	31	1	95
Sucralose—*Limit of hydrolysis products*	31	4	1146
Sucrose—*Harmonization*	31	3	902
Compressible Sugar—*Loss on drying*	31	4	1147
Confectioner's Sugar—*Identification*	31	4	1147
Sunflower Oil (new)	31	1	95
Tagatose (new)	30	5	1672
Medium-Chain Triglycerides—*Definition*	31	1	98
Xylitol—*USP Reference standards, Limit of other polyols, Assay*	31	4	1147

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USP Monographs			
Acepromazine Maleate—*Labeling, Other requirements*	29	6	1832
Acyclovir—*Labeling, USP Reference standards, Other requirements*	30	5	1580
Adenosine—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Medical Air—*Assay*	28	4	1065
Albendazole Oral Suspension—*Labeling*	29	4	991
Albuterol Tablets—*Assay*	31	1	40
Alcohol—*Harmonization*	30	2	670
Dehydrated Alcohol—*Harmonization*	30	2	673
Alfentanil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Alprostadil—*Labeling, USP Reference standards, Other requirements*	29	5	1412
Alteplase—*Labeling, Other requirements*	29	6	1835
Amifostine—*Labeling, USP Reference standards, Other requirements, Assay*	30	6	1974
Aminocaproic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Aminopentamide Sulfate—*Labeling, USP Reference standards, Other requirements*	30	4	1163
Aminophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Amitriptyline Hydrochloride—*Labeling, Other requirements*	29	6	1844
Ammonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1415
Ammonium Molybdate—*Labeling, Other requirements*	29	5	1416
Amphotericin B Lotion—*Title*	30	2	444
Amphotericin B Topical Emulsion (entire submission)	30	2	445
Anileridine—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atenolol—*Labeling, USP Reference standards, Other requirements*	29	5	1416
Atracurium Besylate—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atropine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1847
Aurothioglucose—*Labeling, Other requirements*	29	6	1847
Azaperone—*Labeling, Other requirements*	29	6	1847
Benzoyl Peroxide Lotion—*Title*	30	2	456
Benzoyl Peroxide Topical Emulsion (entire submission)	30	2	456
Benztropine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1848
Benzyl Benzoate Lotion—*Title*	30	2	457
Benzyl Benzoate Topical Emulsion (entire submission)	30	2	457
Betamethasone Tablets—*Identification, Thin-layer chromatographic identification test*	30	1	62
Betamethasone Dipropionate Lotion—*Title*	30	2	458
Betamethasone Dipropionate Topical Emulsion (entire submission)	30	2	459
Betamethasone Valerate Lotion—*Title*	30	2	461
Betamethasone Valerate Topical Emulsion (entire submission)	30	2	461
Bethanechol Chloride—*Labeling, USP Reference standards, Other requirements*	30	5	1586
Biperiden—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Bretylium Tosylate—*Labeling, USP Reference standards, Other requirements*	29	5	1431

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Brompheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1431
Bumetanide—*Labeling, USP Reference standards, Other requirements*	29	5	1432
Bupivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	5	1589
Butorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Caffeine—*Labeling, USP Reference standards, Other requirements*	30	4	1168
Calcium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1436
Carboprost Tromethamine—*Labeling, USP Reference standards, Other requirements*	30	1	82
Carboxymethylcellulose Sodium—*Harmonization*	28	3	867
Chlordiazepoxide Hydrochloride—*USP Reference standards*	29	6	1859
Chloroprocaine Hydrochloride—*Labeling, Other requirements*	29	5	1438
Chloroquine—*Labeling, USP Reference standards, Other requirements*	29	6	1859
Chlorothiazide—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1860
Chromic Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Cimetidine—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Ciprofloxacin Hydrochloride—*Labeling, Other requirements*	29	6	1861
Clonidine Hydrochloride Injection (new)—*Preview*	26	2	351
Clotrimazole Lotion—*Title*	30	2	473
Clotrimazole Topical Emulsion (entire submission)	30	2	474
Codeine Phosphate—*Labeling, USP Reference standards, Other requirements*	30	5	1597
Cortisone Acetate—*Labeling, Other requirements*	29	5	1447
Cupric Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1864
Cupric Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1447
Deslanoside—*Labeling, Other requirements*	29	5	1448
Desmopressin Acetate (new)—*Preview*	24	2	5773
Desmopressin Injection (new)—*Preview*	24	2	5778
Desmopressin Nasal Spray Solution (new)—*Preview*	24	2	5779
Desoxycorticosterone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1456
Desoxycorticosterone Pivalate—*Labeling, USP Reference standards, Other requirements*	29	6	1865
Dexamethasone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Dextran 1—*Other requirements*	29	6	1866
Dextran 40—*Other requirements*	29	6	1866
Dextran 70—*Other requirements*	29	6	1868
Dextrose—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Diatrizoate Meglumine—*Labeling, USP Reference standards, Other requirements*	30	3	832
Diatrizoate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1868

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Diatrizoic Acid—*Labeling, USP Reference standards, Other requirements*	29	6	1869
Diazepam—*Labeling, USP Reference standards, Other requirements*	30	1	96
Diazoxide—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Dibucaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Dicyclomine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Diethylstilbestrol—*Labeling, USP Reference standards, Other requirements*	29	5	1463
Diethylstilbestrol Diphosphate Tablets (entire submission)	30	4	1187
Dihydroergotamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1870
Dimenhydrinate—*Labeling, Other requirements*	29	5	1466
Dimercaprol—*Labeling, Other requirements*	29	5	1466
Diphenhydramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1466
Dipyridamole—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dobutamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dolasetron Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1468
Dopamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1469
Doxapram Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1874
Doxycycline Hyclate—*Content of ethanol*	30	3	836
Droperidol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1875
Dyphylline—*Labeling, USP Reference standards, Other requirements*	29	5	1473
Edetate Calcium Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edetate Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edrophonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1475
Emetine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1875
Ephedrine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	3	840
Epinephrine—*Labeling, USP Reference standards, Other requirements*	29	5	1476
Ergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1478
Ergotamine Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1884
Estradiol—*Labeling, USP Reference standards, Other requirements*	29	5	1478
Estrone—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Ethacrynic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Fenoldopam Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1479
Fentanyl Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1885
Flunixin Meglumine—*Labeling, USP Reference standards, Other requirements*	29	6	1886

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Fluphenazine Decanoate—*Labeling, USP Reference standards, Other requirements*	29	6	1887
Fluphenazine Enanthate—*Labeling, USP Reference standards, Other requirements*	29	6	1887
Fluphenazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1888
Flurandrenolide Lotion—*Title*	30	2	489
Flurandrenolide Topical Emulsion (entire submission)	30	2	489
Fosphenytoin Sodium—*Labeling, Other requirements*	29	6	1888
Fructose—*Labeling, USP Reference standards, Other requirements*	29	5	1496
Furosemide—*Labeling, USP Reference standards, Other requirements*	29	5	1497
Gabapentin (entire submission)	29	1	72
Gadodiamide—*Labeling, Other requirements*	29	6	1889
Gadoteridol—*Labeling, USP Reference standards*	29	6	1890
Gallamine Triethiodide—*Labeling, USP Reference standards, Other requirements*	29	5	1503
Ganciclovir—*Labeling, USP Reference standards, Other requirements*	29	6	1890
Glucagon—*Labeling, USP Reference standards, Other requirements*	30	5	1625
Glycerin—*Labeling, Other requirements*	29	6	1895
Glycopyrrolate—*Labeling, USP Reference standards, Other requirements*	29	5	1503
Gold Sodium Thiomalate—*Labeling, Other requirements*	29	6	1895
Chorionic Gonadotropin—*Labeling*	29	6	1896
Haloperidol—*Labeling, USP Reference standards, Other requirements*	29	6	1897
Helium—*Identification, Assay*	28	4	1121
Histamine Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1504
Hydralazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1505
Hydrocortisone—*Labeling, USP Reference standards, Other requirements*	29	5	1506
Hydrocortisone Lotion—*Title*	30	2	505
Hydrocortisone Topical Emulsion (entire submission)	30	2	506
Hydrocortisone Acetate Lotion—*Title*	30	2	504
Hydrocortisone Acetate Ointment—*Assay*	30	2	504
Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	504
Hydromorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	4	1254
Hydroxyprogesterone Caproate—*Labeling, Other requirements*	29	5	1506
Hydroxyzine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1902
Hyoscyamine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Imipramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1904
Inamrinone—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Indigotindisulfonate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1905
Indinavir Sulfate Capsules (entire submission)	30	2	508
Insulin—*Labeling, Other requirements, Limit of high molecular weight proteins*	30	5	1629
Insulin Human—*Labeling, Other requirements*	29	6	1906

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Inulin—*Labeling, USP Reference standards, Other requirements*	29	6	1906
Iodipamide—*Labeling, USP Reference standards, Other requirements*	29	6	1907
Iodixanol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1908
Iohexol—*Labeling, USP Reference standards, Other requirements*	29	6	1908
Iopamidol—*Labeling, USP Reference standards, Other requirements*	29	6	1909
Iophendylate—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Iothalamic Acid—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Ioversol—*Labeling, USP Reference standards, Other requirements*	29	6	1910
Ioxaglic Acid—*Labeling, Other requirements*	29	6	1911
Ioxilan—*Labeling, Other requirements*	29	6	1911
Isoniazid—*Labeling, USP Reference standards, Other requirements*	29	6	1912
Isoproterenol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1509
Ketamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1913
Ketorolac Tromethamine—*Labeling, USP Reference standards, Other requirements*	29	6	1915
Labetalol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Leuprolide Acetate Injection (new)—*Preview*	25	5	8722
Levorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Levothyroxine Sodium Tablets—*Dissolution, Test 3*	29	3	634
Lidocaine Hydrochloride—*Assay*	30	4	1256
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	30	4	1257
Lindane Lotion—*Title*	30	2	512
Lindane Topical Emulsion (entire submission)	30	2	512
Lorazepam—*Labeling, USP Reference standards, Other requirements*	29	6	1918
†Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (entire submission)	26	4	1050
Magnesium Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1921
Malathion Lotion—*Title*	30	2	513
Malathion Topical Emulsion (entire submission)	30	2	513
Mangafodipir Trisodium—*Labeling, Other requirements*	30	6	2014
Manganese Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1526
Manganese Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1922
Mannitol (entire submission)	27	5	3017
Mannitol Injection (entire submission)	27	5	3020
Mebrofenin—*Labeling, USP Reference standards, Other requirements*	29	6	1923
Medroxyprogesterone Acetate—*Labeling, Other requirements*	29	5	1526
Menadiol Sodium Diphosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1531
Menadione—*Labeling, USP Reference standards, Other requirements*	29	5	1531
Menotropins—*Labeling, Other requirements*	29	6	1923

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Meperidine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1924
Mepivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1533
Mesoridazine Besylate—*Labeling, USP Reference standards, Other requirements*	30	4	1262
Metaraminol Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1533
Methadone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1929
Methocarbamol—*Labeling, USP Reference standards, Other requirements*	29	6	1930
Methohexital—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methotrimeprazine—*Labeling, USP Reference standards, Other requirements*	29	6	1931
Methylbenzethonium Chloride Lotion—*Title*	30	2	515
Methylbenzethonium Chloride Topical Emulsion (entire submission)	30	2	515
Methylbenzethonium Chloride Topical Powder—*Assay*	30	2	516
Methyldopate Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylene Blue—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1535
Methylphenidate Hydrochloride (new)—*Preview*	30	2	731
Methylprednisolone Acetate—*Labeling, Other requirements*	29	5	1535
Metoclopramide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1536
Metoprolol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1536
Metronidazole—*Labeling, USP Reference standards, Other requirements*	29	6	1933
Miconazole—*Labeling, USP Reference standards, Other requirements*	29	6	1934
Morphine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	5	1639
Nalorphine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1935
Naloxone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1936
Nandrolone Decanoate—*Labeling, Other requirements*	29	5	1539
Neomycin Sulfate and Flurandrenolide Lotion—*Title*	30	2	516
Neomycin Sulfate and Flurandrenolide Topical Emulsion (entire submission)	30	2	516
Neomycin Sulfate and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Lotion—*Title*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	519
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519

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Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519
Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neostigmine Methylsulfate—*Labeling, Other requirements*	29	6	1936
Diluted Nitroglycerin—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Norepinephrine Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Nystatin Lotion—*Title*	30	2	522
Nystatin Topical Emulsion (entire submission)	30	2	522
Ofloxacin—*Labeling, USP Reference standards, Other requirements*	30	4	1274
Ondansetron Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1941
Orphenadrine Citrate—*Labeling, USP Reference standards, Other requirements*	30	2	523
Oxandrolone—*Definition, Identification B, Ordinary impurities, Related compounds, Assay*	30	1	148
Oxygen—*Identification, Assay*	28	4	1171
Oxygen 93 Percent—*Identification, Assay*	28	4	1171
Oxymorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1946
Oxytocin—*Labeling, USP Reference standards, Other requirements*	29	6	1946
Paclitaxel—*USP Reference standards, Related compounds (C)*	30	4	1279
Padimate O Lotion—*Title*	30	2	527
Padimate O Topical Emulsion (entire submission)	30	2	527
Papaverine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1551
Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension—*Assay for hydrocortisone acetate*	30	2	528
Pentobarbital—*Labeling, USP Reference standards, Other requirements*	30	1	154
Pentobarbital Sodium—*Labeling, USP Reference standards, Other requirements*	30	1	157
Perphenazine—*Labeling, USP Reference standards, Other requirements*	29	6	1963
Phenobarbital—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phentolamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1562
Phenylbutazone Injection—*USP Reference standards*	29	6	1964
Phenylephrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phenytoin Sodium—*Labeling, USP Reference standards, Other requirements*	30	6	2030
Physostigmine Salicylate—*Labeling, USP Reference standards, Other requirements*	29	6	1967
Potassium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1562
Dibasic Potassium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1563
Prednisolone Acetate—*Labeling, Other requirements*	30	5	1642
Prilocaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1564

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Procainamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1565
Prochlorperazine Edisylate—*Labeling, USP Reference standards, Other requirements*	29	5	1565
Progesterone—*Labeling, Other requirements*	29	5	1566
Promazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1566
Promethazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1567
Propoxycaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	6	2032
Propranolol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Propyliodone—*Labeling, Other requirements*	29	6	1976
Pyridostigmine Bromide—*Labeling, USP Reference standards, Other requirements*	29	6	1977
Quinidine Gluconate—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Ranitidine Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	28	2	360
Reserpine—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Ritodrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Selenious Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1571
Sodium Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1576
Sodium Bicarbonate—*Labeling, USP Reference standards, Other requirements*	29	5	1577
Sodium Nitrite—*Labeling, USP Reference standards, Other requirements*	29	5	1577
Dibasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1578
Monobasic Sodium Phosphate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
Sodium Sulfate—*Labeling, Other requirements*	29	5	1579
Sodium Thiosulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
Sufentanil Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1988
Sulfadiazine Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1988
Sulfamethoxazole—*Labeling, Other requirements*	29	6	1989
Terbutaline Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Terbutaline Sulfate Inhalation Aerosol (entire submission)	26	3	753
Terbutaline Sulfate Injection—*USP Reference standards, Identification, Assay*	26	3	756
Testosterone—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Theophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiopental Sodium—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiothixene Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
Tolazoline Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1588

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Triamcinolone Acetonide—*Labeling, USP Reference standards, Other requirements*	30	3	945
Triamcinolone Acetonide Lotion—*Title*	30	2	538
Triamcinolone Acetonide Topical Emulsion (entire submission)	30	2	538
Trifluoperazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
Triflupromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1994
Trimethobenzamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1589
Trimethoprim—*Labeling, Other requirements*	29	6	1995
Trimethoprim Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1995
Tubocurarine Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1996
Urofollitropin (new) (entire submission)	28	6	1875
Urofollitropin for Injection (new) (entire submission)	28	6	1881
Valproic Acid Injection (new)—*Preview*	26	4	939
Vasopressin—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Verapamil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1598
Xylazine—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Xylazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
Yohimbine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
Zidovudine—*Labeling, USP Reference standards, Other requirements*	29	6	2006
Dietary Supplements Monographs			
Echinacea angustifolia—Microbial limits	30	2	552
Eleuthero—Microbial limits	26	6	1596
Fish Oil Rich in Omega-3 Acids (new) (entire submission)	29	4	1272
Fish Oil Rich in Omega-3 Acids Capsules (new) (entire submission)	29	4	1278
Ginger Capsules—*Microbial limits*	28	3	814
Asian Ginseng—*Microbial limits*	30	2	569
Goldenseal—*Microbial limits*	30	3	952
Licorice—*Microbial limits*	26	5	1363
Powdered Licorice Extract—*Microbial limits*	30	2	574
Shark Liver Oil (new)—*Preview*	26	6	1643
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS	30	6	2092
USP Fluoxetine Related Compound B Solution RS	30	4	1338
USP Methylphenidate Related Compound B RS	30	2	613
USP Methylphenidate Related Compound C RS	30	2	613
USP Methylphenidate Related Compound D RS	30	2	613
USP Methylphenidate Related Compound E RS	30	2	613
USP Methylphenidate Related Compound F RS	30	2	613
USP Methylphenidate Related Compound G RS	30	2	613
USP Methylphenidate Related Compound H RS	30	2	613
USP Paclitaxel Related Compound C RS	30	4	1338
USP Phenylephrine Bitartrate RS	30	3	998
USP Tazobactam Sodium RS	29	3	711
⟨601⟩ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers—*Harmonization*	28	2	584

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⟨621⟩ Chromatography—*Chromatographic Reagents, Phases* (Docosahexaenoic Acid)	29	6	2023
⟨643⟩ Total Organic Carbon (entire submission)	30	5	1700
⟨701⟩ Disintegration—*Harmonization*	28	5	1575
⟨711⟩ Dissolution—*Harmonization*	28	6	1981
⟨776⟩ Optical Microscopy—*Harmonization*	28	2	606
⟨786⟩ Particle Size Distribution by Analytical Sieving—*Harmonization*	28	5	1581
⟨811⟩ Powder Fineness (entire submission)	28	2	611
⟨943⟩ X-Ray Diffraction—Solids (new) (entire submission)	28	3	905
USP General Information Chapters			
⟨1174⟩ Powder Flow (new)—*Harmonization*	28	2	618
⟨1198⟩ Standardized Imprint Codes for Solid Oral Dosage Forms (new)—*Preview*	28	1	152
⟨1225⟩ Validation of Compendial Methods—*Validation—Ruggedness*	30	4	1382
Dietary Supplements Chapters			
⟨2091⟩ Weight Variation of Nutritional Supplements (entire submission)	28	5	1548
Reagents, Indicators, and Solutions			
Air–Nitrous Oxide Certified Standard (added)	28	4	1233
4-Chlorophenol (added)	30	3	1045
Dioleoylglycerol (added)—*Preview*	26	6	1622
Monooleoylglycerol (added)—*Preview*	26	6	1622
Pentadecanoic Acid Methyl Ester (added)—*Preview*	26	6	1622
1,1,4,4-Tetraphenyl-1,3-butadiene (added)	26	6	1623
Trioleoylglycerol (added)—*Preview*	26	6	1623
Reference Tables			
Container Specifications			
Diethylstilbestrol Diphosphate Tablets	30	4	1404
Description and Relative Solubility			
Polydecene (added)	30	4	1405
Excipients			
Polydecene	30	4	1317
NF Monographs			
Adipic Acid—*Packaging and storage*	30	4	1322
Cellaburate—*Packaging and storage*	30	3	967
Microcrystalline Cellulose *(Harmonization)—Packaging and storage*	30	4	1435
Powdered Cellulose *(Harmonization)—Packaging and storage*	30	4	1438
Docosahexaenoic Acid (new)—*Preview*	26	6	1648
Docosahexaenoic Acid Capsules (new)—*Preview*	26	6	1651
Docosahexaenoic Acid Oil (new)—*Preview*	26	6	1652
Ethylparaben *(Harmonization)—Packaging and storage*	30	4	1444
Maltol—*Packaging and storage*	30	3	984
Medium-Chain Triglycerides—*Packaging and storage*	30	3	998
Methylparaben *(Harmonization)—Packaging and storage*	30	4	1446
Nitrogen—*Assay*	28	4	1219
Nitrogen 97 Percent—*Assay*	28	4	1220
†Phenolsulfonphthalein—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94
Phenoxyethanol—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94
Polydecene (entire submission)	30	4	1331

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Polyethylene Glycol (entire submission)—*Preview*	29	4	1313
Propylparaben *(Harmonization)—Packaging and storage*	30	4	1448

†New cancellations in *PF* 31(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 (NF)

BRIEFING

Sodium Starch Glycolate, *NF 23* page 3080 and page 1454 of *PF* 30(4) [July–Aug. 2004]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Sodium Starch Glycolate* 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 on the corresponding monograph for Sodium Starch Glycolate that was prepared by the U.S. Pharmacopeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
pH	+	+	+
Loss on drying	+	+	+
Limit of iron	+	+	+
Limit of sodium chloride	+	+	+
Limit of sodium glycolate	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; – will not stipulate.

Nonharmonized attributes: Characters, Packaging and storage, Labeling, Microbial limits, Heavy metals, Identification by IR absorption.

Specific local attributes: Appearance of solution (EP), ID (sodium flame test) (USP), ID (complies with pH test) (EP).

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

Differences between the Adoption Stage 6 document and the current *NF* monograph include the following:

1. Definition—Modified to be more specific in terms of Type A and Type B.
2. *Packaging and storage*—No change.
3. *Labeling*—Requirements to label indicating Type A or Type B, the botanical source of the starch from which it was derived, and the cross-linking agent are added.
4. *USP Reference standards*—Reference standards for sodium starch glycolate Type A and Type B are added for use with *Identification* test *A*.
5. *Identification*—An IR absorption test and tests for sodium are added.
6. *Microbial limits*—No change.
7. *pH*—Clarification of the requirements for Type A and Type B is added.
8. *Loss on drying*—No change.
9. *Limit of iron*—The test from the EP is adopted.
10. *Heavy metals*—No change.
11. *Limit of sodium chloride*—A simpler procedure using a silver nitrate titration is adopted.
12. *Limit of sodium glycolate*—This test is added to comply with EP standards.
13. *Assay*—No change.

(EMC: J. Lane) RTS—42822-1

Change to read:

~~Sodium Starch Glycolate~~

~~Starch carboxymethyl ether, sodium salt.~~

~~» Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch. It contains not less than 2.8 percent and not more than 4.2 percent of sodium (Na) on the dried, alcohol-washed basis. It may contain not more than 7.0 percent of Sodium Chloride.~~

~~**Packaging and storage**—Preserve in well-closed containers, preferably protected from wide variations in temperature and humidity, which may cause caking.~~

~~**Labeling**—The labeling indicates the pH range.~~

~~**Identification**—A slightly acidified solution of it is colored blue by iodine and potassium iodide TS.~~

~~**Microbial limits** ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*~~

~~**pH** ⟨791⟩—Disperse 1 g in 30 mL of water: the pH of the resulting suspension is either between 3.0 and 5.0 or between 5.5 and 7.5.~~

~~**Loss on drying** ⟨731⟩—Dry it at 130° for 90 minutes: it loses not more than 10.0% of its weight.~~

~~**Iron** ⟨241⟩**:** 0.002%, the *Test preparation* being prepared as directed for *Test preparation* under *Heavy metals, Method III* ⟨231⟩, a 0.5-g test specimen being used and the final solution being diluted with water to 47 mL.~~

~~**Heavy metals,** *Method II* ⟨231⟩**:** 0.002%.~~

~~**Sodium chloride**—Weigh accurately about 1 g, transfer to a conical flask, add 20 mL of 80% alcohol, 0.1 mL of phenolphthalein TS, and 1 N sodium hydroxide solution until the suspension becomes faintly pink, stir for 10 minutes, and filter. Repeat the extraction until chloride has been completely extracted, as shown by a test with silver nitrate TS. Dry the insoluble portion at 105° to constant weight (*A* mg), and reserve it for the *Assay.* Evaporate the combined filtrates, and dry the residue at 105° to constant weight. The weight of the dried residue is not greater than 15% of the weight of Sodium Starch Glycolate taken. If the weight of the dried residue is not more than 7.0% of the weight of Sodium Starch Glycolate taken, the requirement is met. If the weight is greater than 7.0% of the weight of Sodium Starch Glycolate taken, transfer it with the aid of water to a 200-mL volumetric flask, add 5 mL of nitric acid and 40.0 mL of 0.1 N silver nitrate VS, mix, and dilute with water to volume. Allow it to stand in the dark for 30 minutes, and filter. To 100.0 mL of the filtrate add 5 mL of ferric ammonium~~

~~sulfate TS, and titrate with 0.1 N ammonium thiocyanate VS (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Calculate the percentage of sodium chloride by the formula:~~

$$5.844(40N_1 - 2VN_2)/W$$

~~in which N_1 and N_2 are the normalities of the silver nitrate VS and the ammonium thiocyanate VS, respectively, V is the volume, in mL, of ammonium thiocyanate VS used in the titration, and W is the weight, in g, of Sodium Starch Glycolate taken.~~

~~**Assay**—Transfer an accurately weighed portion, *B*, (about 700 mg) of the dried 80% alcohol-insoluble portion obtained in the test for *Sodium chloride*, to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux, on a boiling water bath, for 2 hours, cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Calculate the percentage of sodium combined in the form of sodium starch glycolate by the formula:~~

$$100(22.99)V_2N_2/B$$

~~in which V_2 is the volume, in mL, of the perchloric acid VS, N_2 is the normality of the perchloric acid VS, and B is the weight, in mg, of the dried alcohol-insoluble residue taken for the *Assay*.~~

■Sodium Starch Glycolate

Starch carboxymethyl ether, sodium salt.

» Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0 percent of sodium chloride. The pH and assay requirements for Type A and Type B are set forth in the accompanying table.

	pH		% Sodium, combined as sodium starch glycolate	
Type	Min.	Max.	Min.	Max.
A	5.5	7.5	2.8	4.2
B	3.0	5.0	2.0	3.4

Packaging and storage—Preserve in well-closed containers, preferably protected from wide variations in temperature and humidity, which may cause caking.

Labeling—Label it to indicate the botanical source of the starch from which it was derived, the cross-linking agent (if used), the pH range, and whether it is Type A or Type B.

USP Reference standards ⟨11⟩—*USP Sodium Starch Glycolate Type A RS*. *USP Sodium Starch Glycolate Type B RS*.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: An acidified solution of it is colored blue to violet by the addition of iodine and potassium iodide TS1.

C: To a 2-mL portion of the solution prepared for the test for *Limit of iron,* add 4 mL of *Potassium pyroantimonate solution*. If necessary, rub the inside of the test tube with a glass rod. A white, crystalline precipitate is formed.

Potassium pyroantimonate solution—To 2 g of potassium pyroantimonate add 100 mL of water. Boil the solution for about 5 minutes, cool quickly, and add 10 mL of a solution of potassium hydroxide (3 in 20). Allow to stand for 24 hours, and filter.

D: Sodium starch glycolate imparts an intense yellow color to a nonluminous flame.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*

pH ⟨791⟩—Disperse 1 g in 30 mL of water. The pH of the resulting suspension is either between 5.5 and 7.5 for Type A or between 3.0 and 5.0 for Type B.

Loss on drying ⟨731⟩—Dry it at 130° for 90 minutes: it loses not more than 10.0% of its weight.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Limit of iron—

Standard solution—Dissolve 863.4 mg of ferric ammonium sulfate [$FeNH_4(SO_4)_2 \cdot 12H_2O$] in water, add 25 mL of 2 N sulfuric acid, dilute with water to 500.0 mL, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 1.0 µg of iron per mL.

Test solution—[NOTE—Reserve a portion of this solution for *Identification* test *C.*] Place 2.5 g in a silica or platinum crucible, and add 2 mL of 10 N sulfuric acid. Heat on a water bath, then cautiously raise the temperature progressively over an open flame. Ignite, preferably in a muffle furnace, at 600 ± 25°. Continue heating until all black particles have disappeared. Cool, add a few drops of 2 N sulfuric acid, and heat and ignite as above. Add a few drops of 2 M ammonium carbonate, evaporate to dryness, and ignite as above. Cool, dissolve the residue in 50 mL of water, and mix.

Procedure—Treat the *Test solution* and the *Standard solution* as follows. Transfer 10 mL of the solution to a suitable beaker, add 2 mL of citric acid solution (1 in 5) and 0.1 mL of thioglycolic acid, and mix. Render the solution alkaline, using litmus paper as an external indicator, by the addition of ammonium hydroxide, dilute with water to 20 mL, and mix. Allow the solutions to stand for 5 minutes: the color of the solution obtained from the *Test solution* is a shade of pink no deeper than that of the solution obtained from the *Standard solution* (0.002%).

Limit of sodium chloride—Transfer to a beaker about 500 mg of Sodium Starch Glycolate, accurately weighed, and suspend in 100 mL of water. Add 1 mL of nitric acid. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a suitable silver-based indicator electrode and a double-junction reference electrode containing a 10% potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride.

Limit of sodium glycolate—[NOTE—Conduct this test without exposure to daylight. Use low-actinic glassware.]

Standard solution—Transfer 310 mg of glycolic acid, previously dried over phosphorus pentoxide in a desiccator at room temperature overnight, to a 500-mL volumetric flask, and dissolve in and dilute with water to volume. Transfer 5.0 mL of this solution to a 100-mL beaker, add 4 mL of 6 N acetic acid, and allow to stand for about 30 minutes. Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker and filter paper with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the *Standard solution.*

Test solution—Transfer 200 mg, accurately weighed, to a 100-mL beaker. Add 4 mL of 6 N acetic acid and 5 mL of water. Stir until dissolution is complete (about 10 minutes). Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a 100-mL volumetric flask. Rinse the beaker, and filter with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the *Test solution*.

Procedure—Treat the *Test solution* and the *Standard solution* as follows. Heat 2.0 mL of the solution on a water bath for 20 minutes to remove acetone. Cool to room temperature. Prepare a 2,7-dihydroxynaphthalene solution as follows. Dissolve 10 mg of 2,7-dihydroxynaphthalene in

100 mL of sulfuric acid, allow to stand until decolorized, and use within 2 days. Add 20.0 mL of this 2,7-dihydroxynaphthalene solution to the solution under test, mix, and heat on a water bath for 20 minutes. Cool under running water, and transfer quantitatively to a 25-mL volumetric flask. Maintain the flask under running water, and dilute with sulfuric acid to volume. Within 10 minutes determine the absorbance of the solution at 540 nm with a suitable spectrophotometer, using water as the blank: the absorbance of the solution obtained from the *Test solution* is not more than that of the solution obtained from the *Standard solution* (2.0%).

Assay—Transfer about 1 g to a conical flask, add 20 mL of 80% alcohol, stir for 10 minutes, and filter. Repeat the extraction until the chloride has been completely extracted, as shown by a test with silver nitrate. Dry the insoluble portion at 105° to constant weight, and transfer an accurately weighed portion (about 700 mg) of the dried 80% alcohol-insoluble portion to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux on a boiling water bath for 2 hours, cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Calculate the percentage of sodium combined in the form of sodium starch glycolate by the formula:

$$100(22.99)VN/W$$

in which V is the volume, in mL, of the perchloric acid consumed; N is the normality of the perchloric acid; and W is the weight, in mg, of the dried alcohol-insoluble residue taken for the *Assay*.■2S (*NF24*)

GENERAL CHAPTERS

General Tests and Assays

Chemical Tests and Assays

LIMIT TESTS

BRIEFING

⟨**281**⟩ **Residue on Ignition,** *USP 28* page 2303. The Japanese Pharmacopoeia is the coordinating pharmacopeia in the efforts toward international harmonization of the specifications provided in this general test chapter. The **ADOPTION STAGE 6** text is presented here.

During the development of the Stage 5B Consensus harmonization draft, some differences were noted among the three Pharmacopeial Discussion Group pharmacopeias regarding ignition to constant weight conditions. The *USP–NF* General Notices currently specify 15-minute ignition periods between weighings and a weighing agreement of 0.50 mg per g (of substance taken). The *Japanese Pharmacopoeia* General Notices specify 1-hour ignition periods and a weighing agreement of 0.10%. The *European Pharmacopoeia* specifies an ignition period "appropriate to the nature and quantity of the residue" and a weighing agreement of 0.5 mg. For the purpose of this general chapter only and not for the *USP–NF* General Notices, ignition to constant weight conditions was revised in the Stage 5B Consensus draft to harmonize the ignition time period and weighing agreement parameters for "constant weight" judgment. In the Stage 5B Consensus draft revision, the current *USP–NF* chapter wording of "until constant weight is obtained" has been replaced with the new wording "using a 30-minute ignition period, until two consecutive weighings of the residue do not differ by more than 0.5 mg". That draft revision is contained in the **ADOPTION STAGE 6** text presented herein. This **ADOPTION STAGE 6** text is scheduled for publication in the *Second Supplement* to *USP 29–NF 24,* with a scheduled implementation date of **1 August 2006**.

(PA6: W. Paul) RTS—42664-1

Change to read:

⟨~~281~~⟩ ~~RESIDUE ON IGNITION~~

~~The *Residue on Ignition / Sulfated Ash* test utilizes a procedure to measure the amount of residual substance not volatilized from a sample when the sample is ignited in the presence of sulfuric acid~~

~~according to the procedure described below. This test is usually used for determining the content of inorganic impurities in an organic substance.~~

~~**Procedure**—Weigh accurately 1 to 2 g of the substance, or the amount specified in the individual monograph, in a suitable crucible (silica, platinum, quartz, or porcelain) that previously has been ignited at 600 ± 50° for 30 minutes, cooled in a desiccator (silica gel or other suitable desiccant), and weighed. Moisten the sample with a small amount (usually 1 ml) of sulfuric acid, then heat gently at a temperature as low as practicable until the sample is thoroughly charred. Cool, then, unless otherwise directed in the individual monograph, moisten the residue with a small amount (usually 1 mL) of sulfuric acid, heat gently until white fumes are no longer evolved, and ignite at 600 ± 50°, unless another temperature is specified in the individual monograph, until the carbon is consumed. Ensure that flames are not produced at any time during the procedure. Cool the crucible in a desiccator (silica gel or other suitable desiccant), weigh accurately, and calculate the percentage of residue. Unless otherwise specified, if the amount of the residue so obtained exceeds the limit specified in the individual monograph, repeat the moistening with sulfuric acid, heating and igniting as before, until constant weight is attained or until the percentage of residue complies with the limit in the individual monograph.~~

~~Conduct the ignition in a well-ventilated hood, but protected from air currents, and at as low a temperature as is possible to effect the complete combustion of the carbon. A muffle furnace may be used, if desired, and its use is recommended for the final ignition at 600 ± 50°.~~

~~Calibration of the muffle furnace may be carried out using an appropriate digital temperature meter and a working thermocouple probe calibrated against a standard thermocouple traceable to the National Institute of Standards and Technology.~~

~~Verify the accuracy of the measuring and controlling circuitry of the muffle furnace by checking the positions in the furnace at the control set point temperature of intended use. Select positions that reflect the eventual method of use with respect to location of the specimen under test. The tolerance is ± 25° at each position measured.~~

~~Sulphated Ash tests found in the *European* and *Japanese Pharmacopoeias* are considered equivalent to this test, except where noted.~~

■⟨281⟩ RESIDUE ON IGNITION

Portions of this general chapter have been harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. The portions that are not harmonized are marked with symbols (◆ ◆). The harmonized texts of these pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present *United States Pharmacopeia* general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

The *Residue on Ignition / Sulfated Ash* test uses a procedure to measure the amount of residual substance not volatilized from a sample when the sample is ignited in the presence of sulfuric acid according to the procedure described below. This test is usually used for determining the content of inorganic impurities in an organic substance.

Procedure—Ignite a suitable crucible (for example, silica, platinum, quartz, or porcelain) at 600 ± 50° for 30 minutes, cool the crucible in a desiccator (silica gel or other suitable desiccant), and weigh it accurately. Weigh accurately ◆1 to 2 g of the substance, or ◆ the amount specified in the individual monograph, in the crucible.

Moisten the sample with a small amount (usually 1 mL) of sulfuric acid, then heat gently at a temperature as low as practicable until the sample is thoroughly charred. Cool; then, ◆unless otherwise directed in the individual monograph, ◆ moisten the residue with a small amount (usually 1 mL) of sulfuric acid; heat gently until white fumes are no longer evolved; and ignite at 600 ± 50°, ◆unless another temperature is specified in the individual monograph, ◆ until the residue is completely incinerated. Ensure that flames are not produced at any time during the procedure. Cool the crucible in a desiccator (silica gel or other suitable desiccant), weigh accurately, and calculate the percentage of residue.

Unless otherwise specified, if the amount of the residue so obtained exceeds the limit specified in the individual monograph, repeat the moistening with sulfuric acid, heating and igniting as before, using a 30-minute ignition period, until two consecutive weighings of the residue do not differ by more than 0.5 mg or until the percentage of residue complies with the limit in the individual monograph.

◆Conduct the ignition in a well-ventilated hood, but protected from air currents, and at as low a temperature as is possible to effect the complete combustion of the carbon. A muffle furnace may be used, if desired, and its use is recommended for the final ignition at 600 ± 50°.

Calibration of the muffle furnace may be carried out using an appropriate digital temperature meter and a working thermocouple probe calibrated against a standard thermocouple traceable to the National Institute of Standards and Technology.

Verify the accuracy of the measuring and controlling circuitry of the muffle furnace by checking the positions in the furnace at the control set point temperature of intended use. Select positions that reflect the eventual method of use with respect to location of the specimen under test. The tolerance is ±25° at each position measured.◆■2S (*USP29*)

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).

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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

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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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The Development of Chapter ⟨1235⟩ *Vaccines and Vaccine Test Methods*

Barry D. Garfinkle, John D. Grabenstein, and Joan C. May, *USP Vaccines and Virology Expert Committee;* Roger Dabbah and Tina S. Morris,* *USP Department of Standards Development, Complex Actives Division*

ABSTRACT This *Stimuli* article provides introductory sections and the intended scope of a comprehensive *USP* General Information Chapter on vaccines and vaccine test methods currently under development by the USP Vaccines, Virology, and Immunology Expert Committee. The authors publish this information as a *Stimuli* article with the intent of initiating discussion and public comment. Volunteers to develop these sections and/or review completed sections are welcome and are invited to contact Tina S. Morris, Ph.D., at tsm@usp.org.

VACCINES FOR HUMAN USE: GENERAL INFORMATION CHAPTER ON VACCINES AND VACCINE TEST METHODS

This General Information Chapter provides information about the historical development of the vaccine field, the different types of vaccines currently in use, the most important aspects of vaccine manufacturing processes, and a detailed discussion of vaccine quality control and the tests necessary for the evaluation of the different types of vaccines currently licensed. The chapter is intended to provide useful and relevant background information about vaccines that will amplify information about individual vaccine monographs in the *United States Pharmacopeia (USP).*

INTRODUCTION

Vaccines are among the oldest pharmacologic classes of medications used to combat disease. The first written records on attempts to prevent smallpox by intentional administration of variola virus are attributed to a Buddhist nun practicing in China during the reign of Jen Tsung (1022–1063 AD). In the 7th century, Indian Buddhists attempted to induce immunity through the consumption of snake venom and may have been the first to demonstrate toxoid-like immunity this way. Jenner in 1798 used a preparation from cows infected with cowpox virus to prevent smallpox in humans. His treatise on the causes and effects of the *Variolae vaccinae* is the first scientific and deliberate approach to infection control by systematic inoculation.

A further 87 years elapsed before Pasteur successfully vaccinated humans against rabies. During this period, ideas of microbial attenuation and virulence were developed. Because Jenner himself had shown that immunity through vaccination was not necessarily life long, the idea of revaccination was established and discussed within the scientific community. Two important contributions of Koch were crucial for the further advancement of the field: the conclusive proof of a causal relationship between a bacillus and anthrax disease, and the ability to grow pure cultures of the bacteria. These achievements paved the way for the modern science of vaccination by administration of a specific antigen or infectious agent. The field of vaccinology could not have progressed further without an improved understanding of immunology. In this area Metchnikoff's theory of cellular immunity, published in 1884, as well as Ehrlich's receptor theory of immunity, developed in 1897, were key contributions to the field. Ehrlich also established the difference between active and passive immunity. Thus the major concepts in vaccinology evolved in the late 19th century.

Work in the early 20th century refined these cornerstone theories but advanced dramatically only with the advent of modern cell and tissue culture in the 1930s. The introduction of chorioallantoic membranes of fertilized eggs as a viral growth medium presented a major advance and allowed development of the first killed virus influenza vaccine in 1936, after Laidlaw isolated the influenza A virus from ferrets. The ability to propagate viruses in stationary cell cultures initiated a golden age of viral vaccine development, beginning in 1949. The first licensed vaccine developed by a cell culture technique was Salk's trivalent, formalin-inactivated poliovirus vaccine. It preceded poliovirus vaccines based on live attenuated virus grown in cell culture by several years. However, development of killed or live whole-virus vaccines was often limited by the inability to grow viruses in cell culture in sufficient quantities. For a long time this was the case for hepatitis A virus.

In parallel with rapid developments in vaccines based on whole infectious agents, significant progress was made in subunit or purified antigen vaccines, spearheaded by rapid developments in the area of polysaccharide antigens, probably most notably Pittman's experiments with *Haemophilus influenzae* polysaccharides in the 1930s. Recombinant DNA technology finally allowed the manufacture of vaccines, such as the second-generation hepatitis B vaccine, based on the virus's surface antigen expressed in yeast cells, a development that opened a new era of further technological development in vaccines. Modern vaccines have now been developed for a large number of infectious diseases. The array of technologies available for the development and

manufacture of vaccines, as well as the range of applications, has expanded. Several vaccines currently licensed or under development are not primarily administered to prevent an infectious disease but to fight severe illnesses like cancer, e.g., Bacillus Calmette-Guérin (BCG) live for bladder cancer.

Definitions and Classes

An antigen is a substance capable of inducing an immune response. Vaccines are drug products containing antigenic materials that evoke an acquired immune response in the body. Any macromolecule, as long as it is foreign to the recipient, can function as an antigen. Immune responses may be humoral, cell-mediated, or a combination of both. The antigenic components present in vaccines are processed by the body's immune system, resulting in the development of either serum proteins termed antibodies (i.e., humoral immunity) or specialized lymphocytes (i.e., cell-mediated response). Antibodies are serum proteins able to specifically bind to antigen molecules.

The antibody–antigen binding facilitates the ingestion of the antigen by phagocytic cells and may also activate the complement system that helps destroy the antigen. Antibodies are found primarily in the γ-globulin fraction of plasma and are also referred to as immunoglobulin (Ig). Immunoglobulins are divided into five classes: IgA, IgD, IgE, IgG, and IgM. The Ig classes differ in their structure and primary function and often more than one category of Ig participates in the response to an infectious agent. IgG is a Y-shaped molecule that is comprised of two identical heavy and two identical light chains that are connected by disulfide linkage. Digestion of IgG molecules with the proteinase papain yields two fragments. One fragment, termed Fab, is capable of antigen recognition; the other, called Fc, binds to Fc receptors that are found on the surface of macrophages, neutrophils, and other cells, most notably phagocytes that help eliminate infectious agents. Fc receptor interaction also triggers activation of the complement system via its component C3. The IgA monomer molecule is most important as a secretory antibody, especially at mucosal surfaces. Although the monomer is structurally similar to the IgG molecule, IgA functionally is a dimer linked by a joining (J) chain. IgM is a pentameric molecule, lined by J chains. J chains are additional polypeptide chains of approximately 20 kDa that are produced by IgM-secreting cells. They are covalently inserted between adjacent Fc regions. The pentameric structure allows IgM to recognize antigens composed of identical subunits, like the capsids of viruses. IgM is also a very efficient complement activator. IgD is found in large quantities on the surface of B cells, but it amounts to less than 1% of total serum Ig. An effector function for IgD is not known. IgE is involved in anaphylaxis or immediate hypersensitivity because it occurs with allergies and asthma. IgE is generally found in only small amounts in serum.

All immunoglobulin is secreted by plasma cells. The precursors of these are B-lymphocytes. Each B cell carries a specific Ig receptor for a particular antigen. Once the antigen binds and thus activates this specific cell, it rapidly proliferates, a process that is also called clonal expansion. Clonal expansion results in antibody production, a process that is facilitated by other lymphocytes known as T helper cells. Specific immunoglobulin is mainly produced by plasma cells in the spleen, lymph nodes, and in mucosa-associated lymphoid tissue.

Cell-mediated immune responses are driven by specialized cells that are produced to react with foreign antigens mainly on the surface of host cells. They either directly kill the host cell if the antigen is an infectious agent like a virus, or they recruit other host cells, such as macrophages, to destroy the antigen. The cells responsible for cell-mediated immunity are lymphocytes. They circulate in the blood in very large numbers and are also found in the lymphatic system. A total number of approximately 2×10^{12} lymphocytes circulate the human body. Cellular immune responses are often also mediated by secreted molecules called cytokines (e.g., interleukins and interferons). T lymphocytes can both produce and carry receptors to these factors.

The two major types of immune response, humoral and cellular, are driven by two different classes of lymphocytes. Whereas T cells that develop in the thymus are responsible for cell-mediated immune responses, B cells produce antibodies. All lymphocytes differentiate from pluripotent hematopoietic stem cells. The infection and disease susceptibility of patients with congenital B-cell deficiencies powerfully illustrates the importance of the humoral immune response in fighting infectious diseases.

Cell-mediated immune responses, guided by T cells, are just as antigen-specific as humoral responses, but they do not involve the secretion of antibodies. Different T-cell subpopulations are responsible for different T-cell responses. Once T cells are activated by specific antigens, they begin to divide and differentiate. At least three different responses are possible: (1) T cells directly and specifically kill an infected cell; (2) they help other T or B cells to respond to antigen by recruiting and activating nonlymphocyte cells like macrophages; or (3) they suppress specific T or B lymphocyte responses. Different subpopulations of T cells are responsible for these processes: cytotoxic T cells or killer cells, helper T cells, and suppressor T cells, respectively. T helper and suppressor cells act as regulators of the immune response and hence are often also referred to as regulatory T cells.

Vaccines for human use may contain whole organisms (e.g., bacteria or viruses) or extracts or specific cell products from these organisms as antigens. In addition to antigen(s), vaccines may contain several other components, such as excipients needed for pharmaceutical manufacturing or an adjuvant. Adjuvants help enhance the body's response to a vaccine. Adjuvants come in many forms and may include

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aluminum salts, oil emulsions, and protein conjugates, to name a few. Tests for the most commonly used adjuvants in vaccines today are discussed in the test section of this chapter; for others, the reader is referred to the specific vaccine monograph. Three major types of vaccines—viral, bacterial, and recombinant—are discussed in the following sections.

VIRAL VACCINES

Viral vaccines represent one of the oldest categories of vaccines and include Jenner's live attenuated smallpox vaccine (1798) and Pasteur's rabies vaccine for postexposure treatment (1885). In the modern era, a live poliovirus vaccine was first tested in 1950 but was not licensed until 1960 in the U.S. A cell culture–derived inactivated polio vaccine was licensed in the U.S. in 1955. These polio vaccines are illustrative of the two main types of viral vaccines: live attenuated and killed/inactivated vaccines. Additionally, inactivated virus vaccines may be either whole virus or subunits/substructures of the whole virus. New types of viral vaccines are virosome-based vaccines. An influenza virosome vaccine can be used as an example: antigens (e.g., the influenza virus surface glycoproteins haemagglutinin and neuraminidase) are packaged in a membrane consisting of phospholipids. This virus-like, yet completely replication-incompetent vesicle serves as a delivery device that will fuse with cells of the immune system, where it releases the desired antigen directly. A virosome-based hepatitis A vaccine is licensed in several countries. For traditional viral vaccines, the viruses generally are propagated either in embryonated eggs or various types of tissue culture, including human diploid cells, as well as animal-derived continuous cell lines. Establishment, maintenance, and testing regimens for these cells and cell lines will be described in the respective sections of this chapter.

Live attenuated virus vaccines are based on infection- and replication-competent viruses that will not cause the disease condition in the vaccine recipient. They can confer decades-long immunity after one immunization series but often require repeat doses. They generally are more potent than killed-virus vaccines; however there is a remaining small possibility that after administration they may potentially revert to a more pathogenic form because they can replicate. This risk is very small and can be further reduced by the use of recombinant DNA technology and reverse genetics, for example in the case of live attenuated influenza vaccines. The traditional way to attenuate a virus is by sequential passage in animal cell culture, but there now are more deliberate strategies to achieve attenuation. These include the use of temperature-sensitive strains that do not grow very well in the body, using similar viruses from other species that do not cause the disease in humans, and recombinant viruses developed by infecting cells with several types of viruses simultaneously, resulting in recombinant viruses.

Inactivated virus vaccines are produced by growing the disease-causing strain of virus and then inactivating it so it will not cause infection and replicate in humans. Inactivation may be achieved by treating with heat or chemicals such as formalin, beta propriolactone, or other agents that render the virus replication incompetent. Inactivated viral vaccines include whole virus and subunit vaccines. Inactivated viral vaccines require successful cultivation of the virus in a human or animal cell line to achieve sufficient quantities, which is crucial and not always easy to achieve. An inactivated hepatitis A vaccine remained elusive for a long time for this reason. Many subunit vaccines, on the other hand, have become easier and less expensive to manufacture since the advent of recombinant DNA technology. The second-generation hepatitis B vaccine (HBV) is a good example. In this case the HBV surface antigen is expressed in recombinant yeast cells. The success of a subunit vaccine, however, generally depends on a good understanding of the immunogenic properties of the different components of the virus. Especially in the case of emerging diseases this is not always the case.

BACTERIAL VACCINES

The development of bacterial vaccines dates to the late 19th century, when experimental typhoid, plague, and cholera vaccines were first made. As with viral vaccines, both live attenuated and inactivated or killed bacterial vaccines have been developed. The first bacterial vaccines that were developed were all killed vaccines. Bacterial toxins of tetanus and diphtheria were detoxified and turned into toxoid vaccines in the 1920s. BCG vaccine was the first attenuated live bacterial vaccine (1927). Attenuation was achieved over 13 years and 230 passages in beef bile. After the 2nd World War an attenuated *Salmonella typhi* strain became available. Just as in the case of viral attenuated vaccines, live attenuated bacterial vaccines are strains of bacteria that are very similar to the disease-causing strain but do not produce disease. This may be because they contain antigens similar to those in the disease-causing strain but do not produce a disease-causing toxin or because they are an entirely different organism that contains antigens that cross-react with the virulent strain of bacteria.

Inactivated bacterial vaccines are produced by growing cells of the disease-causing bacteria and subsequently inactivating them to prevent replication in the body of the recipient. The bacteria may be inactivated with heat or chemicals. There are many types of inactivated bacterial vaccines, including whole-cell and subunit vaccines. Whole-cell vaccines consist of the entire microorganism once it has been inactivated. These preparations may or may not be purified or partially purified. Subunit vaccines are extracts from the inactivated bacteria consisting of cell complexes, extracted polysaccharides, proteins, lipids, or toxins produced by the microorganisms in question. The subunit-type vaccines generally undergo some degree of purification. These extracts are normally produced using different types of chemical or physical separation. A specific type of vaccine is made from the toxins from the bacteria, which are treated chemically to render the toxin inactive but still immunogenic, allowing this so-called toxoid to stimulate an immune

response so the body will inactivate toxin produced by the disease-causing microorganisms. Another very common type of bacterial subunit vaccine is the polysaccharide vaccine, for which different cell surface and cell wall polysaccharides of disease-causing bacteria are purified and used as antigenic material. Especially during the 1970s and 1980s several bacterial vaccines consisting of purified capsular polysaccharides were developed, for example meningococcal group A and C vaccines. Pneumococcal polysaccharide vaccine development started in the early 1940s and continues to this day, resulting in vaccines that contain more than twenty different antigen types.

BIOTECHNOLOGY-DERIVED VACCINES

Several types of vaccines against viral or bacterial infections are derived by these techniques.

Recombinant Cellular Factories

The first category uses genetically modified bacteria or yeast cells for the recombinant expression of antigenic material. These host cells have been transformed with expression vectors carrying genes that encode antigenic material from either viral or bacterial infectious agents. The expression cells are grown in bioreactors to produce the recombinant antigenic material. This antigenic material is purified from the culture media using a variety of chemical and physical separations. Purified recombinant antigens can be proteins, glycoproteins, or protein–lipid complexes. Further, they may be either soluble preparations or may assemble/be assembled into structures such as empty viral capsids. These capsids consist of a viral shell structure but do not contain any viral genetic material. An advantage of this type of vaccine is that it does not have to contain the entire viral genome, hence avoiding the risk of the vaccine containing replication-competent disease-causing virus. Subunit or recombinant protein vaccines derived by biotechnology processes have the advantage that the components contained in the vaccine as well as the materials used in the cell culture of the hosts are very well defined and can be extensively characterized. However, to be successful they require extensive research and knowledge of the antigenic properties of the target infectious agent.

Nucleic-Acid Vaccines

A second type of vaccine strategy, the DNA vaccine, involves the creation of a DNA plasmid that contains one or several, but not an entire set, of genes from the disease-causing agent. The plasmid vector contains genes encoding the antigenic material from the infectious agent, along with necessary promoters and other genetic controls. The plasmid is produced in an expression host such as a bacterial culture and is purified. Once purified DNA is introduced into the body of the vaccine recipient, it enters selected cells and begins to express the genes encoded by the expression plasmid and stimulates the immune system in a manner similar to using the viral vector described previously. This type of vaccine is not yet commercially available.

Viral Vectors

A third type of biotechnology-derived vaccine involves modifying a virus by insertion of one or several—but not an entire set—of genes from a disease-causing virus. This modified virus is a so-called viral vector for the expression of antigens from a different infectious agent. The modified virus can then infect an individual and in replicating within the cells of the body produces the foreign antigens from the disease-causing virus. The viral vector used is itself often replication-deficient. The immune system then responds to these antigens with a humoral and/or cell-mediated response.

Conjugate Vaccines

Conjugate vaccines are often utilized as a strategy when the immune response to the antigen itself is weak and the conjugation provides a method to increase the antigenicity and therefore the immune response to the antigen. Conjugate vaccines take advantage of the knowledge that often both B cells and T cells need to work together to stimulate a sufficient immune response. This strategy has been utilized primarily in combining bacterial polysaccharides, e.g., *H. influenzae,* pneumococcal, or meningococcal polysaccharides, with various bacterial proteins. These proteins have come from tetanus toxoid, modified diphtheria toxin, and meningococcal outer membrane protein. The conjugation results in a binding of the polysaccharide antigen to one of these carrier materials. Conjugate vaccines are a direct development of research conducted with both purified antigens as well as bacterial capsule polysaccharides. These vaccines are manufactured by combining an antigen with additional materials extracted from microorganisms to render the material more immunogenic.

Multivalent Vaccines

Early vaccines typically were univalent in nature, which means that they contained only one particular antigen. However, many current vaccines contain multiple antigens from different strains of the organism that causes a clinical disease. Most notable are influenza vaccine (three types), poliovirus vaccine (three serotypes), meningococcal vaccine (four serogroups), and pneumococcal vaccines (7 or 23 types). The multivalency normally is utilized when a disease is caused by a number of different strains of an organism and no common antigen results in strong immunity. Therefore, a vaccine is developed to contain strain-specific antigens to convey immunity to the disease.

Combination Vaccines

These vaccines are the result of combining vaccines against two or more infectious diseases into a single drug product. Positive aspects of these products are improved compliance because fewer visits to a health professional are required, and economic advantages accrue because only one administration, i.e., injection, is required. Parents also appreciate that fewer visits are required to implement the vaccination schedules that have become more complicated as more vaccines have become available. The majority of combination vaccines are aimed at the pediatric market, e.g. MMR (measles, mumps, and rubella), DTP (diphtheria, tetanus, and pertussis), etc.

Adjuvants

These are compounds with which antigens are combined to improve the immune response. Numerous adjuvants exist and include aluminum hydroxide, aluminum phosphate, aluminum hydroxyphosphate, aluminum potassium sulfate, mineral oil/aqueous emulsions, and protein conjugates, to name a few.

PLANNED CHAPTER SECTIONS CURRENTLY UNDER DEVELOPMENT

The following outline provides an overview of the sections of proposed General Information Chapter ⟨1235⟩ *Vaccines and Vaccine Test Methods.*

General considerations for vaccine development, manufacturing, and quality control

- Production
  - — General provisions
  - — Substrates for propagation
  - — Seed lots
  - — Culture media
  - — Propagation and harvest
  - — Purification
  - — Inactivation
  - — Intermediates
  - — Final bulk
  - — Adjuvants
  - — Antimicrobial preservatives
  - — Stabilizer
  - — Surface-active agents
  - — Final lot
  - — Stability
  - — Packaging and storage
  - — Expiration
  - — Nomenclature and labeling

General vaccine tests applicable to all types of vaccines

- Tests for antimicrobials
- Tests for adjuvants
- Tests for inactivating agents
- Tests for stabilizers
- Tests for surface-active agents
- Tests for dyes
- Tests for medium components and ancillary materials
- Tests for miscellaneous excipients and residuals

Protein Vaccines

- Introduction
- Simple and complex proteins: description and definition
  - — Recombinant antigens, inactivated toxins/toxoids
  - — Multicomponent vaccines (e.g., acellular pertussis vaccine)
  - — Brief principles of manufacturing methods; different steps (general)
    - — Development and maintenance of master and working seeds
    - — Fermentation
      - — Different cell lines
    - — Purification
      - — Precipitation
      - — Chromatography
      - — Other methods
    - — Detoxification (inactivated toxins and toxoids)
    - — Formulation: stability and other considerations (such as long-term stability, stinging, allergic reaction, preservative, etc.)
  - — Stability and storage
- Tests
  - — Total protein
  - — SDS-PAGE
  - — Western blot
  - — Capillary electrophoresis
  - — Chromatographic procedures
  - — Immunochemical methods
  - — ELISA
  - — Antigen-to-mass ratio
  - — Potency

Polysaccharide Vaccines

- Special characteristics
  - — Bacterial
  - — Ti, IgM, little immunity in infants
    - — Different types
    - — Brief principles of manufacturing methods; different steps (general)
  - — Development and maintenance of master and working seeds
    - — Cell growth
    - — Purification
      - — Solvent fractionation
      - — Chromatography
      - — Other methods
    - — Formulation: stability and other considerations
  - — Stability and storage
- Tests

Polysaccharide–Protein Conjugate Vaccines
- Purpose of conjugation: target population
- Different types of proteins/peptides used in conjugation
- Manufacturing methods (outline)
  - — Spacer arm
  - — Activation
  - — Conjugation; polysaccharide to protein ratio
  - — Capping
  - — Removal of unconjugated polysaccharide
  - — Formulation: stability and other considerations
  - — Stability and storage
- Tests

Viral Vaccines
- Live attenuated vaccines
  - — Attenuation strategies
  - — Manufacturing methods
  - — Stability and storage
  - — Tests
  - — Safety
- Inactivated vaccines
  - — Inactivation strategies
  - — Manufacturing methods
  - — Stability and storage
  - — Tests
  - — Safety

Bacterial Vaccines
- Live attenuated vaccines
  - — Attenuation strategies
  - — Manufacturing methods
  - — Stability and storage
  - — Tests
  - — Safety
- Inactivated vaccines
  - — Inactivation strategies
  - — Manufacturing methods
  - — Stability and storage
  - — Tests
  - — Safety

Combination Vaccines

DNA Vaccines

Viral Vectors

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.

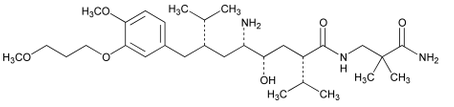
USP Dictionary of USAN and International Drug Names
2005 USP DICTIONARY SUPPLEMENT 2

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

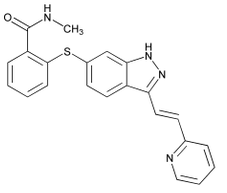
Newly Approved United States Adopted Names (USAN), Released for Publication

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.

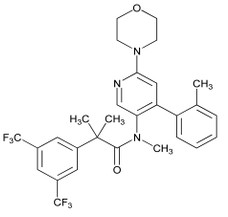
Aliskiren [*2005*] (a lis′ kir en″). $C_{30}H_{53}N_3O_6$. 551.76. (1) Benzeneoctanamide, δ-amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)-, (α*S*, γ*S*, δ*S*, ζ*S*)-; (2) (2*S*,4*S*,5*S*,7*S*)-5-Amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonamide.*CAS-173334-57-1*. INN. *Treatment of essential hypertension* (*renin inhibitor*). (Novartis Pharma AG, Switzerland) ✧*SPP100*



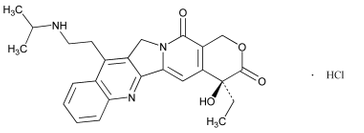
Axitinib [*2005*] (ax″ i ti′ nib). $C_{22}H_{18}N_4OS$. 386.50. (1) Benzamide, *N*-methyl-2-[[3-[(1*E*)-2-(2-pyridinyl)ethenyl]-1*H*-indazol-6-yl]thio]-; (2) *N*-Methyl-2-[[3-[(1*E*)-2-(pyridin-2-yl)ethenyl]-1*H*-indazol-6-yl]sulfanyl]benzamide. *CAS-319460-85-0*. *Antineoplastic, inhibitor of VEGF/PDGF tyrosine kinases.* (Pfizer) ✧*AG-013736*



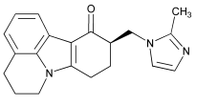
Befetupitant [*2005*] (bef″ et ue′ pi tant). $C_{29}H_{29}F_6N_3O_2$. 565.60. (1) Benzeneacetamide, *N*,α,α-trimethyl-*N*-[4-(2-methylphenyl)-6-(4- morpholinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-; (2) 2-(3,5-Bis(trifluoromethyl)phenyl)-*N*-[4-[2-methylphenyl]-6-(morpholin-4-yl)pyridin-3-yl]-*N*-methylisobutyramide. *CAS-290296-68-3*. INN. *Treatment of depression.* (Hoffmann-LaRoche) ✧*Ro 67-5930*



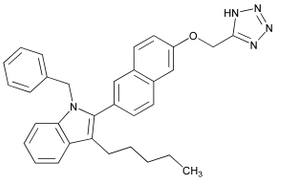
Belotecan Hydrochloride [*2005*] (bel″ oh tee′ han). $C_{25}H_{27}N_3O_4$.HCl. 469.97. [Belotecan is INN.] (1) 1*H*-Pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione, 4-ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-, monohydrochloride, (4*S*)-; (2) (4*S*)-4-Ethyl-4-hydroxy-11-[2-[(1-methylethyl)amino]ethyl]-1,12-dihydro-14*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*)-dione hydrochloride. *CAS-213819-48-8; CAS-256411-32-2* [belotecan]. *Antineoplastic* (*DNA topoisomerase I inhibitor*). (Boehringer Ingelheim Chemicals) ✧*CKD-602*



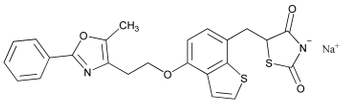
Cilansetron [*2005*] (sil an se′ tron). $C_{20}H_{21}N_3O$. 319.40. (1) 4*H*-Pyrido[3,2,1-jk] carbazol-11 (8*H*)-one, 5,6,9,10-tetrahydro-10-[(2-methyl-1*H*-imidazol-1-yl) methyl]-, (10*R*)-; (2) (10*R*)-5,6,9,10-Tetrahydro-10[(2-methylimidazol-1-yl)-methyl]-4*H*-pyrido[3,2,1-jk]carbazol-11(8*H*)-one. *CAS-120635-74-7*. INN. *Treatment of irritable bowel syndrome.* (Solvay Pharmaceuticals) ✧*KC-9946*



Diaplasinin [*2005*] (dye a plas′ in in). $C_{32}H_{31}N_5O$. 501.60. (1) 1*H*-Indole, 3-pentyl-1-(phenylmethyl)-2-[6-(1*H*-tetrazol-5-ylmethoxy)-2-naphthalenyl]-; (2) 1-Benzyl-3-pentyl-2-[6-(1*H*-tetrazol-5-ylmethoxy)naphthalen-2-yl]-1*H*-indole. *CAS-481631-45-2*. *Treatment of fibrinolytic impairment diseases.* (Wyeth) ✧*PAI-749*

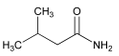


Edaglitazone Sodium [*2005*] (ed″ a gli′ ta zone).
$C_{24}H_{19}N_2NaO_4S_2$. 486.50. [Edaglitazone is INN.] (1) 2,4-Thiazolidinedione, 5-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzo[b]thien-7-yl]methyl]-, sodium salt; (2) Sodium(5*RS*)-5-[[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1-benzothiophen-7-yl]methyl]-2,4-dioxothiazolidin-3-ide.-*CAS-369631-81-2; CAS-213411-83-7* [edaglitazone]. *Treatment of Type 2 diabetes.* (Hoffmann-LaRoche) ✧*RO2052349-602*

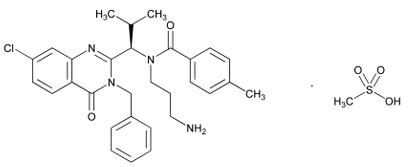


Ipilimumab [*2005*] (i pi lim′ ue mab). $C_{6472}H_{9972}N_{1732}O_{2004}S_{40}$. Immunoglobulin G1, anti-(human CTLA-4 (antigen)) (human γ1-chain), disulfide with human κ-chain, dimer. Molecular weight is approximately 145,400 daltons. *CAS-477202-00-9. Treatment of oncology disease and HIV infection.* (Medarex) ✧*MDX-010; MDX-CTLA-4*

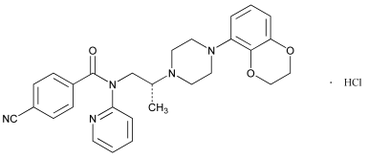
Isovaleramide [*2005*] (eye″ soe val er′ a mide). $C_5H_{11}NO$. 101.15. (1) Butanamide, 3-methyl-; (2) 3-Methylbutanamide. *CAS-541-46-8. Anxiolytic, anticonvulsant, antispastic, antimigraine, mood stabilizer and analgesic.* (NPS) ✧*NFS1776*



Ispinesib Mesylate [*2005*] (is pin′ es ib). $C_{30}H_{33}ClN_4O_2.CH_4O_3S$. 613.20. [Ispinesib is INN.] (1) Benzamide, *N*-(3-aminopropyl)-*N*-[(1*R*)-1-[7-chloro-3,4-dihydro-4-oxo-3-(phenylmethyl)-2-quinazolinyl]-2-methylpropyl]-4-methyl-, monomethanesulfonate; (2) *N*-(3-Aminopropyl)-*N*-[(1*R*)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-methylpropyl]-4-methylbenzamide monomethanesulfonate. *CAS-514820-03-2; CAS-336113-53-2* [ispinesib]. *Antineoplastic* (*kinesin inhibitor*). (GlaxoSmithKline) ✧*SB-715992-S; CK0238273*



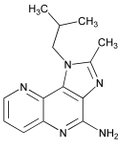
Lecozotan Hydrochloride [*2005*] (le koe′ zoe tan).
$C_{28}H_{29}N_5O_3.HCl$. 520.00. (1) Benzamide, 4-cyano-*N*-[(2*R*)-2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)-1-piperazinyl]propyl]-*N*-2-pyridinyl-, monohydrochloride; (2) 4-Cyano-*N*-[(2*R*)-2-[4-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazin-1-yl]propyl]-*N*-(pyridin-2-yl)benzamide monohydrochloride. *CAS-433282-68-9. Treatment of cognitive deficits associated with Alzheimer's disease* (5-HT_{1A} receptor antagonist). (Wyeth) ✧*SRA-333*



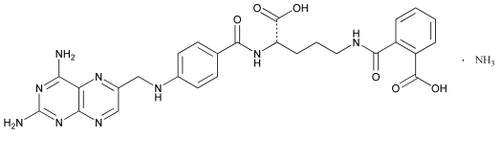
Mapatumumab [*2005*] (map″ a toom′ ue mab).
$C_{6388}H_{9856}N_{1712}O_{1998}S_{46}$. (1) Immunoglobulin G1, anti-(human cytokine receptor DR4 (death receceptor 4)) (human monoclonal TRM-1 heavy chain), disulfide with human monoclonal TRM-1 λ-chain, dimer; (2) Immunoglobulin G1, anti-(human TRAIL-R1) (human monoclonal TRM-1 heavy chain), disulfide with human monoclonal TRM-1 λ-chain, dimer. *CAS-658052-09-6. Treatment of cancer.* (Human Genome Sciences) ✧*TRAIL-R1 mAb; TRM-1; HGS-ETR1*

Perflubutane [*2005*] (per floo′ bue tane). C_4F_{10}. 238.00. (1) Butane, decafluoro-; (2) Decafluorobutane. *CAS-355-25-9*. INN. *Ultrasound contrast agent intended for assessing myocardial perfusion in patients with coronary artery disease.* (Acusphere) ✧*AI-700*

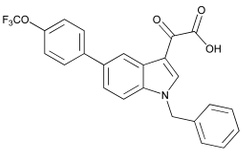
Sotirimod [*2005*] (soe tir′ i mod). $C_{14}H_{17}N_5$. 255.30. (1) 1*H*-Imidazo[4,5-*c*][1,5]naphthyridin-4-amine, 2-methyl-1-(2-methylpropyl)-; (2) 2-Methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. *CAS-227318-75-4. Treatment of dermatologic diseases, including actinic keratosis, infections, cancer.* (3M Pharmaceuticals) ✧*R-850; S-30594*



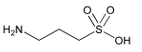
Talotrexin Ammonium [*2005*] (tal oh trex′ in). $C_{27}H_{27}N_9O_6.H_3N$. 590.60. (1) Benzoic acid, 2-[[[(4*S*)-4-carboxy-4-[[4-[[(2,4-diamino-6-pteridinyl)methyl]amino]benzoyl]amino]butyl]amino]carbonyl]-, monoammonium salt; (2) 2-[[(4*S*)-4-Carboxy-4-[[4-[[(2,4-diaminopteridin-6-yl)methyl]amino]benzoyl]amino]butyl]carbamoyl]benzoic acid monoammonium salt. *CAS-648420-92-2. Antineoplastic.* (HANA Biosciences) ✧*PT-523; PT523; NSC-712783*



Tiplasinin [*2005*] (ti plas′ in in). $C_{24}H_{16}F_3NO_4$. 439.38. (1) 1*H*-Indole-3-acetic acid, α-oxo-1-(phenylmethyl)-5-[4-(trifluoromethoxy)phenyl]-; (2) [1-Benzyl-5-[4-(trifluoromethoxy)-phenyl]-1*H*-indol-3-yl]oxoacetic acid. *CAS-393105-53-8. Treatment of fibrinolytic impairment diseases.* (Wyeth) ✧*PAI-039*



Tramiprosate [*2005*] (tram ip′ roe sate). $C_3H_9NO_3S$. 139.20. (1) 1-Propanesulfonic acid, 3-amino-; (2) 3-Aminopropane-1-sulfonic acid. *CAS-3687-18-1. Treatment of mild-to-moderate Alzheimer's disease, treatment of cerebral amyloid angiopathy.* (Neurochem) ✧*NC-758*

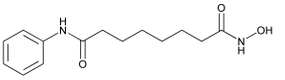


Velafermin [*2005*] (vel′′ a fer′ min). $C_{1047}H_{1632}N_{306}O_{302}S_5$. Fibroblast growth factor?20 (human recombinant CG53135). Molecular weight is approximately 23,500 daltons. *CAS-697766-75-9. Treatment and/or prevention of mucositis.* (CuraGen) ✧*CG53135-05*

MAPLAEVGGF LGGLEGLGQQ VGSHFLLPPA GERPPLLGER RSAAERSARG
GPGAAQLAHL HGILRRRQLY CRTGFHLQIL PDGSVQGTRQ DHSLFGILEF
ISVAVGLVSI RGVDSGLYLG MNDKGELYGS EKLTSECIFR EQFEENWYNT
YSSNIYKHGD TGRRYFVALN KDGTPRDGAR SKRHQKFTHF LPRPVDPERV
PELYKDLLMY T

Volociximab [*2005*] (voe loe six′ i mab). $C_{6434}H_{9942}N_{1706}O_{2040}S_{52}$. Immunoglobulin G4, anti-(human α5β1 integrin) (human-mouse clone p200-M heavy chain), disulfide with human-mouse clone p200-M κ-chain, dimer. *CAS-558480-40-3. Antiangiogenic agent to treat solid tumors and age-related macular degeneration.* (ICOS) ✧*M200*

Vorinostat [*2005*] (vore in′ oh stat). $C_{14}H_{20}N_2O_3$. 264.32. (1) Octanediamide, *N*-hydroxy-*N′*-phenyl-; (2) *N*-Hydroxy-*N′*-phenyloctanediamide. *CAS-149647-78-9. Antineoplastic, histone deacetylase inhibitor.* (Merck)



United States Adopted Names (USAN) Under Consideration

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.

USAN Under Consideration	Category
Acaftadine	*H1 receptor antagonist*
Afavatadine	
Alacaftadine	
Alcaftadine	
Avnactadine	
Adariconazole	*Antifungal agent*
Alconazole	
Camaconazole	
Peloconazole	
Pirconazole	
Zoconazole	
Adopanib Hydrochloride	*Antineoplastic*
Balitanib Hydrochloride	
Pazopanib	
Pazopanib Hydrochloride	
Afetegrant	*Treatment of multiple sclerosis, inflammatory bowel disease*
Alfortegral	
Alitegrant	
Firategrant	
Fortegratag	
Afinoxifene	*Treatment of breast cancer*
Quatroxifene	

USAN Under Consideration	Category
Aldismasem	*Anti-inflammatory and antimicrobial; SOD mimetic*
Imisopasem	
Insopasem Manganese	
Modismasem	
Selanzymin	
Selezymin	
Selmimase	
Selmimetase	
Somimase	
Somimetase	
Sopasemim Manganese	
Sumimetase	
Suprozymin	
Zormimase	
Alfortegral	*Treatment of multiple sclerosis*
Fortegratag	
Anthrotrisox Sodium	*Antineoplastic*
Avotrilid Sodium	
Omatrilid Sodium	
Oxotrisox Sodium	
Sunatrilid Sodium	
Apadenoson	*An adjunct to nuclear myocardial perfusion imaging in patients unable to exercise adequately*
Arcadenoson	
Filadenoson	
Miladenoson	
Paladenoson	

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

USAN Under Consideration	Category
Aplaviroc Pelacriviroc Hydrochloride Pelaviroc Hydrochloride Sirocrivoc Hydrochloride Siroviroc Hydrochloride	*Treatment of HIV infection*
Aralonacept Arilonacept Iralonacept Ralonacept Rilonacept	*Treatment of rheumatoid arthritis, autoinflammatory diseases and osteoarthritis*
Aramatinib Dasatinib Dasmaintinib Sabexitinib Sarbextinib	*Anxiolytic; anticonvulsant; antispastic; antimigraine; mood stabilizer; analgesic; treatment of cancer*
Azepropilmycin Prazamycin Propazamycin	*Veterinary antibacterial*
Azoramib Olaramib Petoramib Petorozole Tolarozole Zolramib Zoramib	*Treatment of keratinization disorders, acne and psoriasis*
Aztreonam Lysinate	*Management of Pseudomonas aeruginosa infection*
Becatadine Belatadine Benatadine Dihydrochloride Piratadine Dihydrochloride Pivatadine Zoltadine Dihydrochloride Zoratadine Dihydrochloride	*Treatment of atopic dermatitis*
Bidelukast Bitelukast Milolukast	*Treatment of asthma and interstitial cystitis*
Brifospofol Disodium Brifosprofol Disodium Fospropofol Fospropofol Disodium Prefospofol Disodium Profospofol Disodium Propofol Phosphate Disodium	*Intravenous sedative-hypnotic solution in conscious sedation for brief surgical and diagnostic procedures*
Brilipladib Bripladib Corbilipladib Goxalapladib Orbilipladib	*Treatment of atherosclerosis*
Cangrelor	*Antiplatelet agent*
Casipitant Mesylate Casopitant Clasipitant Mesylate	*Treatment of depression, anxiety, sleep disorders, nausea and vomiting, functional dyspepsia, irritable bowel syndrome, gastroesophageal reflux disease and overactive bladder disease*
Cetforlimumab Cetinlimumab Cetlalimumab Cetolimumab Citilimumab Ticilimumab	*Treatment of cancer*
Cidfusituzumab IL-2 Cidtuzumab Cidtuzumab IL-2 Cidtuzumab Interleukin-2 Cidtuzumabkin IL-2 Eczumabkine Epcamabkin Epcamkinab Epkinzumab Pecfusituzumab IL-2 Pectumuzmab IL-2 Pectuzumab Pectuzumab Interleukin-2 Pectuzumabkin IL-2 Tucotuzumab Celmoleukin Tuctuzumab Tuctuzumab IL-2 Tuctuzumab Interleukin-2 Tuctuzumabkin IL-2 Tucusituzumab IL-2	*Treatment of cancers of epithelial origin*
Cynostumab Cynotumumab Denostumab Denosumab Denotumumab Genostumab Synostumab	*Prevention and treatment of all forms of osteoporosis or bone loss*
Darapladib Darlapladib Goxalipladib Oxalipladib Voxalipladib	*Treatment of atherosclerosis*
Decripentoc Dicripentoc Vicripentoc Vicriviroc	*Antiviral; CCR5 antagonist; treatment of autoimmune conditions*
Delamostat Golamostat Relacatib Relamostat Zelamostat	*Treatment of osteoporosis*
Denagliptin Denogliptin Tosylate	*Treatment of type II diabetes*
Desancycline Incemocline Incyclinide Incyclinor Incymastat Incyplemib Intepacib Inteplemib Maztecinor	*Treatment of rosacea; treatment of acute respiratory distress syndrome (ARDS); (chemically modified tetracycline [CMT]) which is claimed to inhibit multiple proteases and cytokines*

USAN Under Consideration	Category
Dexamfetamine Lysine Dimesylate	*Treatment of ADHD (central nervous system stimulant)*
Dextroamphetamine Lysine Dimesylate	
Lidamfetamine Dimesylate	
Lidamphetamine Dimesylate	
Lidetamine Dimesylate	
Lidexamfetamine Dimesylate	
Lidextroamphetamine Dimesylate	
Lifentamine Dimesylate	
Lisamfetamine Dimesylate	
Lisdexamfetamine	
Diaplaginin	*Treatment of fibrinolytic impairment disease*
Diaplasginin	
Diaplasinin	
Diaplastinin	
Diaplaxtinin	
Difirolimus	*Antineoplastic*
Dofosirolimus	
Gifosirolimus	
Safosirolimus	
Torolimus	
Eiriflapon	*Prevention of acute cardiovascular events*
Eriflapon	
Loxiflapon	
Veliflapon	
Eltrombopag	*Treatment of chemotherapy-induced thrombocytopenia and iodiopathic thrombocytopenic purpura*
Eltrombopan Diolamine	
Etrobopan Diolamine	
Gemcaristim	
Getrobopan Diolamine	
Megprocaristim	
Recepcaristim	
Retrombopan Diolamine	
Xelcaristim	
Zexcaristim	
Elzivadose Hydrochloride	*Treatment of Fabry disease*
Elzydavose Hydrochloride	
Fabenimose Hydrochloride	
Migalastat	
Emevatide	*Melanoma peptide vaccine; treatment of cancer*
Omatide	
Omevatide	
Ovemotide	
Vamevatide	
Fingolimod	*Prevention of organ rejection in patients receiving allogenic renal transplants*
Fingolimod Hydrochloride	
Fosaprepitant	*Antiemetic; substance P antagonist (neurokinin NK1 antagonist)*
Fosaprepitant Dimeglumine	
Fulvotaxel	*Treatment of NSCLC and metastatic breast cancer*
Misotaxel	
Naltotaxel	
Simotaxel	
Hioxifilcon D	*Contact lens*

USAN Under Consideration	Category
Imicrocidem	*Treatment of malaria, African Sleeping Sickness, and Pneumocystis Pneumonia*
Muramidem Maleate	
Muramidine Maleate	
Prilamidem Maleate	
Prilamidine Maleate	
Proparacidem	
Tripicidem	
Tropamidem Maleate	
Tropamidine Maleate	
Iobomipic acid I 123	*Diagnostic imaging agent*
Iodofazic acid I 123	
Iodofenate	
Iodofenoate	
Iofantic acid I 123	
Iofenoate	
Iofofiltic acid I 123	
Iratumumab	*Treatment of oncologic diseases; treatment of relapsed or refractory CD30 positive lymphoma including Hodgkin's disease*
Resatumumab	
Restumumab	
Rosutumumab	
Tiratumumab	
Tritumumab	
Lacosamide	*Treatment of epilepsy and pain*
Levamlodipine Maleate	*Treatment of hypertension*
Lexitumumab	*Antineoplastic*
Trixatumumab	
Vexatumumab	
Mamotide Sodium	*Treatment of osteosarcoma*
Memotide Sodium	
Mepactide	
Mepactide Sodium	
Muratide	
Muratide Sodium	
Murimotide Sodium	
Mepactide	*Treatment of osteosarcoma*
Muratide	
Motavizumab	*Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk*
Motovizumab	
Nolovizumab	
Numavizumab	
Ralivizumab	
Reslivizumab	
Resyvizumab	
Umavizumab	
Obatoclax	*Treatment of cancer*
Oraptoclax Mesylate	
Raptobeclib Mesylate	
Pasomilast	*Treatment of atopic dermatitis*
Pramilast	
Primilast	
Promilast	
Rimilast	
Zomilast	
Recipanib	*Age-related macular degeneration*
Versanib	
Visrefanib	

USAN Under Consideration	Category
Rotigaptide	*Treatment of ventricular tachycardia or ventricular fibrillation*
Rotiregap	
Sapropterin Hydrochloride	*Treatment of PKU*
Sarizotan Hydrochloride	*Schizophrenia, Parkinson's disease*

International Nonproprietary Names (INN) Under Consideration

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 ensures 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.

(INN) Under Consideration	Category
Acaftadine Alcaftadine	*H1 receptor antagonist*
Adarolimus Tezorolimus Zotarolimus Zoterolimus	*Antifungal macrolide (drug component of an investigational phosphoryl choline polymer coated eluting stent, currently under evaluation for the prevention of coronary restenosis following stent replacement)*
Apadenoson Paladenoson	*Adjunct to nuclear myocardial perfusion imaging in patients unable to exercise adequately*
Aplaviroc Pelaviroc Hydrochloride	*Treatment of HIV infection*
Arblurbifenil Arflurbiprofen	*Antineoplastic; treatment of Alzheimer's disease*
Brilapladib Bripladib	*Treatment of atherosclerosis*
Casipitant Mesylate Casopitant	*Treatment of depression, anxiety, sleep disorders, nausea and vomiting, functional dyspepsia, irritable bowel syndrome, gastro-esophageal reflux disease, and overactive bladder disease*
Citilimumab Ticilimumab	*Treatment of cancer*
Darapladib Darlapladib	*Treatment of atherosclerosis*
Denagliptin Denogliptin Tosylate	*Treatment of type II diabetes*
Denosumab	*Treatment of osteoporosis*
Diaplaginin Diaplasginin Diaplasinin Diaplastinin Diaplaxtinin	*Treatment of fibrinolytic impairment disease*
Eltrombopag	*Treatment of chemotherapy-induced thrombocytopenia and treatment of idiopathic thrombocytopenic purpura*
Elzivadose Hydrochloride Migalastat	*Treatment of Fabry disease*
Fosaprepitant Fosaprepitant Dimeglumine	*Antiemetic; substance P antagonist (neurokinin NK1 antagonist)*
Fospropofol Fospropofol Disodium	*Sedative-hypnotic*
Incyclinide Incyplemib	*Treatment of rosacea and acute respiratory stress*
Insopasem Manganese Sopasemim Manganese	*Treatment of pain and inflammation (superoxide dismutase mimetic)*
Iratumumab Tiratumumab	*Treatment of relapsed or refractory CD30 positive lymphona*
Lidetamine Dimesylate Lisdexamfetamine	*Treatment of ADHD*
Misotaxel Simotaxel	*Treatment of NSCLC and metastatic breast cancer*
Motavizumab Motovizumab	*Prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk*

Nomenclature

(INN) Under Consideration	Category
Obatoclax Oraptoclax Mesylate	*Treatment of cancer*
Omevatide Ovemotide	*Melanoma peptide vaccine; treatment of cancer*
Relacatib Relamostat	*Treatment of osteoporosis*
Rotigaptide Rotiregap	*Treatment of ventricular tachycardia or ventricular fibrillation*
Tepribavirin Vabavirin	*Antiviral, pro-drug of ribavirin*
Tiplactinin Tiplasinin Tiplastinin Tiplaxtinin	*Treatment of fibrinolytic impairment diseases*
Tucotuzumab Celmoleukin	*Treatment of cancers of epithelial origin*
Vicriviroc	*Antiviral; CCR5 antagonist; treatment of autoimmune conditions*

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 31(1).

[*Note—This index covers Vol. 31 No. 1, pp. 1–288, Vol. 31, No. 2, pp. 289–669, Vol. 31, No. 3, pp. 671–980, Vol. 31, No. 4, pp. 981–1287, Vol. 31, No. 5, pp. 1289–1556*]

GENERAL NOTICES AND REQUIREMENTS

MONOGRAPHS

EXCIPIENTS

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Reagent Specifications

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Chromatographic Reagents Used in *USP–NF* and *Pharmacopeial Forum*

Sept.–Oct. 2005

No records shown for this month.

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 _____

Address _____

_____

_____

Telephone No. ( ) _____
(area code)

*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 a update based on the proposals published in this issue of *PF*.

Chromatographic Reagents Used in *USP–NF* and *Pharmacopeial Forum*

Sept.–Oct. 2005

No records shown for this month.

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PHARMACOPEIAL FORUM VOL. 31 NO. 6 NOV.–DEC. 2005

* The *USP–NF* (*USP29–NF24*), 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*).

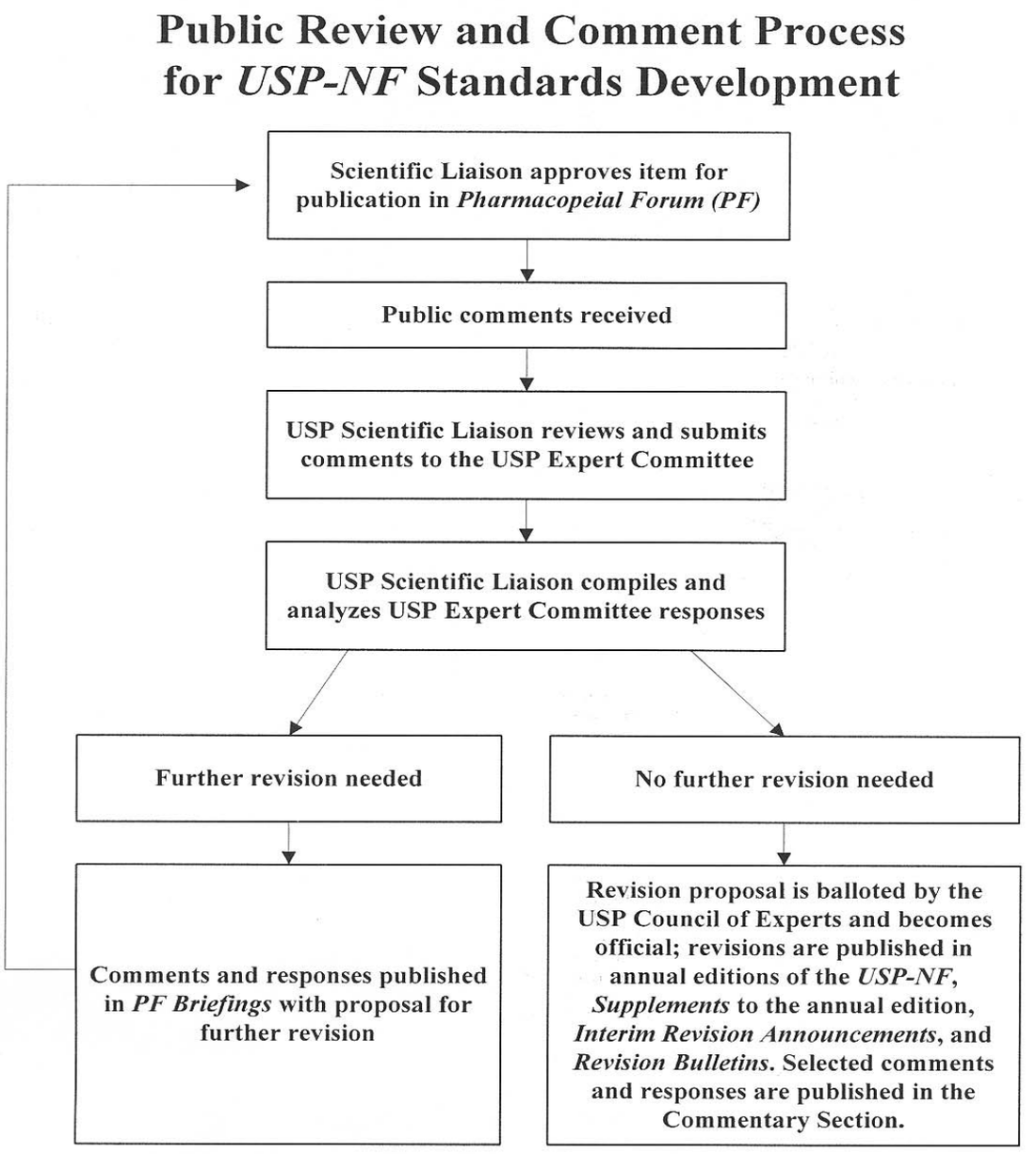
PF includes the following:

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.



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@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 content of the different sections of *PF* are briefly described below. 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 in the *Guideline for Submitting Requests for Revision to the USP-NF* on the USP website (http://www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP-NF*

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 working 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.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

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
- Where to find 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* 31(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:

2000—2005

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
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EMC	Excipient Monograph Content
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 7a—Antibiotics; 7b—Antimicrobials and Antivirals
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

2005—2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell and Gene Therapy
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding

2005—2010 (*Continued*)

RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

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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. This section also includes publication and comment schedules.

USP SEEKS SUBMISSION OF PROPOSALS FOR STABILITY INDICATING ASSAY PROCEDURES FOR STEROIDS. The procedures for assay for steroids in many *USP–NF* monographs are not stability indicating. In an effort to update the monographs, the Monograph Development—Pulmonary and Steroids Expert Committee is seeking submission of proposals of stability indicating assay procedures for steroids, preferably HPLC- or GC-based, for inclusion in the following *USP–NF* monographs to replace the current procedures that are not stability indicating. The submissions should include data and other information recommended in the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf. Each submission should include analytical validation data, data demonstrating that the procedure is stability indicating, and results of analysis from three commercial batches.

Please submit proposals for steroid assay procedures for the following *USP–NF* monographs to Dr. Daniel Bempong or contact him for the details at 301-816-8143 or dkb@usp.org.

Drug Substance:

Clocortolone Pivalate
Danazol
Desoxycorticosterone Acetate
Estriol
Fludrocortisone Acetate
Flumethasone Pivalate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate
Hydroxyprogesterone Caproate
Levonorgestrel
Meprednisone
Mestranol
Methylprednisolone Sodium Succinate
Nandrolone Phenpropionate
Norethindrone
Norethindrone Acetate
Norethynodrel
Norgestrel
Oxandrolone
Oxymetholone
Paramethasone Acetate
Prednisolone Hemisuccinate
Prednisolone Sodium Phosphate
Testosterone
Testosterone Enanthate
Testosterone Propionate

Dosage Form:

Betamethasone Oral Solution
Clocortolone Pivalate Cream
Desoxycorticosterone Acetate Injection
Desoxycorticosterone Acetate Pellets
Dexamethasone Gel
Dexamethasone Sodium Inhalation Aerosol
Dexamethasone Tablets
Dexamethasone Topical Aerosol
Estradiol Injectable Suspension
Estradiol Tablets
Estrone Injection
Flumethasone Pivalate Cream
Hydrocortisone Acetate Injectable Suspension
Hydrocortisone Acetate Ophthalmic Ointment
Hydrocortisone Acetate Ophthalmic Suspension
Hydrocortisone Injectable Suspension
Hydrocortisone Sodium Phosphate Injection
Hydroxyprogesterone Caproate Injection
Methylprednisolone Acetate Cream
Methyltestosterone Capsules
Methyltestosterone Tablets
Nandrolone Phenpropionate Injection
Norethindrone Acetate Tablets
Norethindrone Acetate and Ethinyl Estradiol Tablets (assay for both steroids)
Norethindrone Tablets
Norgestrel Tablets
Oxymetholone Tablets
Paramethasone Acetate Tablets
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable Suspension (assay for Prednisolone)
Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment (assay for Prednisolone Acetate)
Prednisolone Sodium Phosphate Injection
Prednisolone Sodium Phosphate Ophthalmic Solution
Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment (assay for Prednisolone Sodium Phosphate)
Prednisolone Sodium Succinate for Injection
Prednisolone Cream
Progesterone Intrauterine Contraceptive System
Testosterone Enanthate Injection
Testosterone Injectable Suspension
Testosterone Propionate Injection

CALL FOR HIGH PRIORITY MONOGRAPHS FOR DRUG SUBSTANCES AND PRODUCTS AND EXCIPIENTS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below (updated as of September 1, 2005).

Monograph sponsors should consult the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf.

For further information, contact Karen Russo, Ph.D., kar@usp.org.

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine	Anagrelide Hydrochloride ***(Received)***	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bicalutamide ***(Received)***	Bivalirudin
Budesonide ***(Received)***	Cabergoline	Calcipotriene
Calcium Trisodium Pentetate	Calfactant	Candesartan Cilexetil
Carmustine	Carvedilol	Cefdinir
Cefditoren Pivoxil	Ceftibuten	Cetirizine Hydrochloride
Cetrorelix	Cevimeline	Chloroxine
Cilostazol ***(Received)***	Citalopram Hydrobromide ***(Received)***	Colfosceril
Cytarabine Liposome	Dalfopristin	Dantrolene Sodium ***(Received)***
Dapirazole Hydrochloride	Desirudin	Dexrazoxane
Didanosine ***(Received)***	Difloxacin Hydrochloride	Divalproex Sodium ***(Received)***
Docosanol	Entacapone	Epoprostenol
Erythromycin Phosphate	Erythromycin Thiocyanate	Esomeprazole Magnesium
Esmolol	Estazolam	Estramustine Phosphate Sodium
Estradiol Benzoate	Ethanolamine Oleate	Etomidate
Etoposide Phosphate	Exemestane	Felbamate
Fentanyl ***(Received)***	Fluoromethane F 18	Foscarnet Sodium
Fosfomycin Tromethamine	Gadobenate Dimeglumine	Galantamine
Gadopentetic Acid	Gallium Nitrate	Ganirelix
Glyceryl Aminobenzoate	Granisetron	Halobetasol Propionate
Haloperidol Decanoate ***(Received)***	Hydrocodone Polistirex	Hydrocortisone ***(Received)***
Ibandronate Sodium	Imipramine Pamoate	Imiquimod
Irinotecan	Isosulfan Blue	Itraconazole
Lamotrigine	Latanoprost	Lawsone
Levetriacepam	Levobetaxolol	Levocabastine Hydrochloride
Levofloxacin ***(Received)***	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Miglitol	Mifepristone	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide	Nedocromil
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium	Orbifloxacin
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pancuronium Bromide ***(Received)***
Pantoprazole Sodium	Pemoline	Pentamidine Isethionate
Piperonyl Butoxide	Pirbuterol Acetate	Poractant Alpha
Prednicarbate ***(Received)***	Proguanil	Quetiapine Fumarate
Risperidone ***(Received)***	Rose Bengal	Salmeterol Xinafoate
Sodium Phenylbutyrate	Simethicone ***(Received)***	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride	Terconazole	Tiludronate Disodium

Noncomplex Actives (Drug Substances) *(Continued)*

Tiopronin	Tranexamic Acid	Trimipramine Maleate
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate, and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Amlodipine and Benazepril Hydrochloride Capsules	Aminopterin Sodium Tablets
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution
Bivalirudin Injection	Budesonide Metered-Dose Inhalation Aerosol	Budesonide Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochlorides Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules
Butalbital and Acetaminophen Tablets	Butorphanol Tartrate Nasal Solution ***(Received)***	Calcipotriene Topical Solution Cabergoline Tablets
Calcipotriene Cream	Calcipotriene Ointment	Calcitriol Capsules
Calcitriol Oral Solution	Calcium Acetate Capsules	Calfactant Intratracheal Suspension
Calcium Trisodium Pentetate Injection	Carbidopa and Levodopa Extended-Release Tablets	Carbidopa and Levodopa Tablets for Oral Suspension
Carbidopa, Levidopa, and Entacapone Tablets	Carmustine Implant	Carmustine for Injection
Carvedilol Tablets	Cefditoren Pivoxil Tablets	Cefdinir Tablets
Ceftibuten Capsules	Ceftibuten for Oral Suspension	Cetirizine Hydrochloride Oral Solution
Ceftiofur Hydrochloride Oral Suspension	Cetrorelix Injection	Cetirizine Hydrochloride Tablets
Cevimeline Hydrochloride Capsules	Choline and Magnesium Salicylates Oral Solution	Chloroxine Cream
Chlorpromazine Hydrochloride Extended-Release Capsules	Ciclopirox Shampoo	Choline and Magnesium Salicylates Tablets
Choline Salicylate Oral Solution	Ciclopirox Topical Gel	Ciclopirox Topical Solution
Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Cilostazol Tablets	Cimetidine Oral Solution
Citalopram Hydrobromide Oral Solution	Citalopram Hydrobromide Tablets ***(Received)***	Ciprofloxacin Otic Solution
Cladribine Injection	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Clonazepam Orally Disintegrating Tablets
Clemastine Fumarate Syrup	Clobetasol Propionate Gel	Clotrimazole and Betamethasone Dipropionate Lotion

Noncomplex Actives (Drug Products) *(Continued)*

Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets	Colfosceril and Tyloxapol Suspension
Colestipol Hydrochloride Tablets	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Compound Undecylenic Acid Cream
Compound Undecylenic Acid Topical Powder	Cyclosporine Modified Oral Solution	Cromolyn Sodium Metered-Dose Nasal Solution
Cyclosporine Modified Capsules	Cysteamine Bitartrate Capsules	Cyclosporine Ointment
Cyclosporine Topical Solution	Cytarabine Liposome Injection	Dantrolene Sodium Capsules ***(Received)***
Dalfopristin and Quinupristin Injection	Dapiprazole for Ophthalmic Solution	Dantrolene Sodium for Injection ***(Received)***
Dantrolene Sodium Oral Suspension	Desirudin for Injection	Desonide ***(Received)***
Desonide Cream	Dexrazoxane for Injection	Dextroamphetamine Sulfate Extended-Release Capsules
Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable	Diclofenac Sodium Ophthalmic Solution
Didanosine Chewable Tablets ***(Received)***	Didanosine for Oral Solution ***(Received)***	Diethylpropion Hydrochloride Extended-Release Tablets
Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray
Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution
Doxacurium Chloride Injection	Doxepin Hydrochloride Cream	Doxycycline Oral Gel
Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection	Emulsion
Enalaprilat Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Entacapone Tablets	Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection
Epoprostenol Injection	Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules
Estazolam Tablets	Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection
Etomidate Injection	Etidronate Disodium Injection Concentrate	Exemestane Tablets
Famotidine Injection	Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension
Felbamate Tablets	Fentanyl Lozenges	Fentanyl Transdermal System
Ferrous Fumarate and Docusate Sodium Extended- Release Capsules	Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets
Fluconazole Injection	Flunisolide Nasal Spray	Fluconazole Tablets
Flunisolide Inhalation Aerosol	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluticasone Propionate Inhalation Powder	Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets
Gadobenate Dimeglumine Injection	Gallium Nitrate Injection	Galantamine Hydrobromide Tablets
Ganirelix Acetate Injection	Ganciclovir Capsules	Gentamicin Sulfate Oral Solution
Gatifloxacin Injection	Gatifloxacin Tablets	Glipizide Extended-Release Tablets
Gentamicin Sulfate Soluble Powder	Glimepiride Tablets	Granisetron Tablets
Granisetron Injection	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution
Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Ointment
Halobetasol Propionate Cream	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution

Noncomplex Actives (Drug Products) *(Continued)*

Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrochlorothiazide Capsules
Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets	Hydrocortisone Butyrate Lotion
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	Hydrocortisone Acetate Rectal Foam Aerosol	Hydroquinone Lotion
Hydrocortisone Acetate Dental Paste	Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution
Ibuprofen Capsules	Ibandronate Sodium Tablets	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules
Ketoprofen Extended-Release Capsules	Ketotifen Fumarate	Ketotifen Fumarate Ophthalmic Solution
Ketoprofen Tablets	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Levetriacepam Tablets	Levobetaxolol Ophthalmic Suspension
Levocabastine Ophthalmic Suspension	Leucovorin Calcium for Injection	Levomethadyl Acetate Hydrochloride Oral Concentrate
Levofloxacin Solution	Lidocaine and Prilocaine Cream ***(Received)***	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder
Liothyronine Injection	Lisinopril And Hydrochlorothiazide Tablets	Lomustine Capsules
Lopinavir Capsules	Lopinavir Solution	Lopinavir and Ritonavir Solution
Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***	Loratadine Orally Disintegrating Tablets	Losartan Potassium Tablets
Mesalamine Suppositories	Methacholine Chloride for Inhalation Solution	Mesoridazine Besylate Concentrate
Mefloquine Hydrochloride Tablets	Methoxsalen Softgels	Methadone Hydrochloride Oral Concentrate
Melphalan for Injection	Metaraminol Bitartrate Injection	Methyclothiazide and Deserpidine Tablets
Methocarbamol and Aspirin Tablets	Metipranolol Ophthalmic Solution	Metronidazole Cream
Metronidazole Lotion	Metronidazole Extended-Release Tablets	Methylphenidate Hydochloride Chewable Tablets
Metronidazole Capsules	Midazolam Hydrochloride Injection	Metronidazole Hydrochloride for Injection
Miconazole Nitrate Topical Aerosol	Mifepristone Tablets	Miglitol Tablets
Milrinone Injection	Misoprostol Dispersion ***(Received)***	Misoprostol Tablets ***(Received)***
Mivacurium in Dextrose Injection	Mivacurium Injection	Moexipril Hydrochloride and Hydrochlorothiazide Tablets
Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution	Morphine Sulfate for Injection Concentrate
Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate	Morphine Sulfate Tablets
Mycophenolate Mofetil Tablets	Mycophenolate Mofetil Oral Solution	Mycophenolate Mofetil Capsules
Nalbuphine Hydrochloride Injection	Naproxen Extended-Release Tablets	Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution	Nalmefene Hydrochloride Injection	Nateglinide Tablets
Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder	Nevirapine Oral Suspension
Nevirapine Tablets ***(Received)***	Nicardipine Hydrochloride Capsules	Nilutamide Tablets
Nimodipine Capsules	Nisoldipine Extended-Release Tablets	Nitroglycerin Solution in Acrylic Adhesive
Nizatidine Tablets	Ofloxacin Injection	Ofloxacin in Dextrose Injection
Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution	Olsalazine Sodium Capsules
Ondansetron Oral Solution	Ondansetron Tablets	Orbifloxacin Tablets
Orlistat Capsules ***(Received)***	Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Orphenadrine Citrate Extended-Release Tablets
Oxcarbazepine Suspension	Oxcarbazepine Tablets	Oxiconazole Cream

Noncomplex Actives (Drug Products) *(Continued)*

Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium Tablets	Pantoprazole Sodium for Injection
Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension	Pemirolast Potassium Ophthalmic Solution
Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution	Pentaerythritol Tetranitrate Extended-Release Capsules
Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation	Pentamidine Isethionate for Injection
Pentazocine Hydrochloride and Acetaminophen Tablets	Permethrin Cream	Phendimetrazine Tartrate Extended-Release Capsules
Phenobarbital Capsules	Phentermine Resin Complex	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules
Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Phentermine Resin Complex Capsules	Phosphate Oral Solution
Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment	Pilocarpine Hydrochloride Tablets
Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol	Povacrylate Solution
Poractant Alpha Supension	Porfimer Sodium for Injection	Povacrylate-Iodine Topical Solution
Povidone-Iodine Gauze	Povidone-Iodine Swabsticks	Povidone-Iodine Topical Aerosol Foam
Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets	Prazosin Hydrochloride and Polythiazide Capsules
Prednicarbate Cream ***(Received)***	Prednicarbate Ointment ***(Received)***	Prednisolone Sodium Phosphate Oral Solution
Prochlorperazine Maleate Extended-Release Capsules	Progesterone Capsules	Promethazine Hydrochloride and Codeine
Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup
Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets
Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets
Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pyrilamine Maleate Injection
Quinidine Sulfate Injection	Ramipril Capsules	Ranitidine Capsules
Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets	Rimantadine Hydrochloride Oral Solution
Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets	Risperidone Tablets
Rivastigmine Tartrate Capsules	Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection
Ropinirole Hydrochloride Tablets	Rose Bengal Ophthalmic Solution	Rosiglitazone Maleate Tablets
Salicylic Acid and Sulfur Cleansing Lotion	Salicylic Acid and Sulfur Lotion	Salicylic Acid and Sulfur Shampoo
Salicylic Acid Cream	Salicylic Acid Ointment	Salmeterol Inhalation Aerosol
Salmeterol Xinafoate Inhalation Powder	Scopolamine Transdermal System	Selegiline Hydrochloride Capsules
Serpacwa Topical Cream	Sertraline Hydrochloride Oral Solution	Sibutramine Hydrochloride Capsules
Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Sodium Chlorophyllin Copper Complex Tablets
Sodium Iodide Injection	Sodium Phenylbutyrate Oral Powder	Sodium Phenylbutyrate Tablets
Sodium Phosphates for Oral Suspension	Sodium Phosphates Tablets	Sodium Salicylate and Sulfur Shampoo
Sterile Talc Aerosol	Streptozocin for Injection	Sucralfate Oral Suspension
Sulconazole Nitrate Cream	Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension

Noncomplex Actives (Drug Products) *(Continued)*

Sulfacytine Tablets	Sulfanilamide Vaginal Cream	Sulfasalazine Oral Suspension
Sumatriptan Tablets	Sulisobenzone Lotion	Sumatriptan Injection
Tacrolimus Capsules	Tacrolimus Ointment	Tacrolimus Injection
Tamsulosin Hydrochloride Capsules	Technetium Tc 99M Teboroxime Injection	Tenofovir Disoproxil Fumarate Tablets
Terbinafine Hydrochloride Cream	Terbinafine Tablets	Terbinafine Topical Solution
Terconazole Vaginal Cream	Terconazole Vaginal Suppositories	Testosterone Transdermal System
Tetracycline Hydrochloride Periodontal Fiber	Theophylline Extended-Release Tablets	Tioconazole Vaginal Ointment
Tiopronin Tablets	Tolnaftate Topical Aerosol Solution	Topiramate Capsules
Topiramate Tablets	Torsemide Injection	Torsemide Tablets
Trandolapril and Verapamil Hydrochloride Extended-Release Tablets	Trandolapril Tablets	Tranexamic Acid Injection
Tranylcypromine Sulfate	Tranylcypromine Sulfate Tablets	Tretinoin Capsules
Tretinoin Microsphere Gel	Triamcinolone Acetonide Metered-Dose Nasal Suspension	Trifluridine Ophthalmic Solution
Trimetrexate for Injection	Trimipramine Maleate Capsules	Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup
Trolamine Salicylate Cream	Trolamine Salicylate Gel	Trolamine Salicylate Topical Emulsion
Trovafloxacin Injection	Trovafloxacin Mesylate for Injection	Undecylenic Acid Topical Foam Aerosol
Unoprostone Isopropyl Ophthalmic Solution	Urea Cream	Valproic Acid Injection ***(Received)***
Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules	Venlafaxine Tablets
Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection
Voriconazole Oral Suspension	Voriconazole Tablets	Yttrium Y-90 Chloride Solution
Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection	Ziprasidone Hydrochloride Capsules
Zidovudine and Lamivudine Tablets	Zinc Acetate Capsules	Zoledronic Acid for Injection
Zinc Tridosium Pentetate Injection		

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	*N*-Acetyl-L- Methionine
Aconitic Acid (Achilleic Acid)	Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal
Aliphatic Polyesters	Aluminum Ammonium Sulfate	Aluminum Hydroxide
Aluminum Lactate	Aluminum Oxide	Aluminum Ammonium Sulfate
Aluminum Potassium Sulfate	Aluminum Silicate	Aluminum Sodium Sulfate
Aluminum Stearate	Allantoin-Sodium Pyrrolidone Carboxylate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	L-Ascorbyl Stearate
L-Asparagine	Batylalcohol Monostearate	Beeswax, Synthetic
Benzododecinium Bromide	Benzyl Chloride	Benzyl Nicotinate
Brominated Vegetable Oil	Butadiene- Styrene Rubber	Beta Naphthol
Butylene Glycol	Butylphthalyl Butylglycolate	Butylated Hydromethylphenol
Calcium Alginate	Calcium Alginate and Ammonium Alginate	Calcium Acid Pyrophosphate
Calcium Chloride Solution	Calcium Glycerophosphate	Calcium Bromide
Calcium Phosphate Dibasic, Monohydrate	Calcium Phosphate Monobasic	Calcium Phosphate Dibasic, Anhydrous
Calcium Pyrophosphate	Calcium Sorbate	Calcium Propionate
Calcium Sulfate Dihydrate	Calcium Sulfate, Anhydrous	Calcium Stearoyl Lactylate
Calteridol Calcium	Canola Oil	Caldiamide Sodium
Caprylic/Capric Diglyceril Succinate	Carbon	Capric Acid
Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium	Carboxymethyl Starch
Cetostearyl Isononanoate	Cholic Acid	Cinnamaldehyde
Chlorodifluoroethane	Cocamide Diethanolamine	Cocamide Oxide

Excipients *(Continued)*

Coconut Oil Hydrogenated	Cocoyl Caprylocaprate	Coconut Oil
Crystal Gum	Cutina	Copper Sulfate
L-Cysteine Monohydrochloride	Dammar Gum	Cystine
Decanoic Acid	Decyl Oleate	Dehydroacetic Acid
Desoxycholic Acid	Dextrin Palmitate	Dextrins Modified
Diacetyl Tartaric Acid Esters of Mono- and Diglycerides	Dicetyl Phosphate	Dichlorofluoromethane
Diethylene Glycol Monopalmitostearate	Diethyl Sebacate	Difluoroethane
Diglycol Stearate	Diisopropanolamine ***(Received)***	Diisobutyl Adipate
Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate
Dimethyl Dicarbonate	Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol
Dioctyl Sodium Sulfosuccinate	Dipropylene Glycol	Disodium Edisylate
Disodium Guanylate	Disodium Inosinate	Disodium Monooleamide Sulfasuccinate
Docusate Sodium/Sodium Benzoate	Erythritol ***(Received)***	Erythorbic Acid
Erythrosine	Ethoxylated Mono- and Diglycerides	Ethoxyquin
Ethyl Hexanediol	Ethyl Linoleate	Ethyl Maltol
Ethylene Dichloride	Ethylene Glycol Monopalmitostearate	Ethylurea
Ferric Ammonium Citrate	Ferric Citrate	Ferric Oxide, Brown
Ferric Phosphate	Ferric Pyrophosphate	Ferrous Citrate
Ferrous Glycinate	Ferrous Lactate	Fluorochlorohydrocarbons
Formic Acid	Furcelleran	Gamma-Cyclodextrin
Gentistic Acid	Geraniol	L-Glutamic Acid
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydrogenated Starch Hydrolysate	Hydroxyethylmethylcellulose
Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin	Indigotine
Inositol	Iron Carbonyl	Iron Subcarbonate
Isobutylated-Isoprene Copolymer	Isooctylacrylate	Isopropyl Isostearate
Isopropyl Stearate	Isostearic Acid	Isostearyl Alcohol
Lactobionic Acid	Lactose Ferrin, Bovine	Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol
Lactylic Esters of Fatty Acids	Lanolin Anhydrous	Lanolin Alcohols, Acetylated
Lanolin (Wool Fat), Hydrogenated	Lanolin Hydrous	Lauramine Oxide
Lauric Acid	Lauric Diethanolamide	Lauric Myristic Diethanolamide
Lavender Oil	Lecithin, Hydroxylated	L-Leucine
Linoleic Acid	Macrogol Lauryl Ether	Macrogol Oleate
Macrogol Sorbitan Tristearate	Macrogol Stearyl Ether	Macrogolglycerol Cocoates
Macrogolglycerol Triisostearate	Magnesium Aluminum Silicate Hydrate	Magnesium Aspartate
Magnesium Aspartame Dihydrate	Magnesium Phosphate, Dibasic, Trihydrate	Magnesium Phosphate Tribasic
Magnesium Tartrate	Maltitol ***(Received)***	Maltitol Syrup
Maltol Isobutyrate	Malt Syrup	Manganese Chloride
Manganese Citrate	Manganese Glycerophosphate	Manganese Hypophosphite
D-Mannose	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methyl Hydroxyethyl Cellulose	Methylisothiazolinone	*N*-Methylpyrrolidone ***(Received)***
Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits	Monoisostearyl Glyceryl Ester
Monopotassium Glutamate Monohydrate	Monosodium Citrate	Mullein Leaf
Myristyl Gamma-Picolinium Chloride	Myristyl Lactate	*N*,*N*-Bis(2-Hydroxyethyl)Stearamide
Naphtha	Non-Pareil Seeds	Nutmeg Oil

Excipients *(Continued)*		
Octanoic Acid	Oleyl Oleate ***(Received)***	Oxystearin
Palm Kernel Oil	Palm Oil	Pentasodium Triphosphate
Pentetate Calcium Trisodium	Pentetate Pentasodium	Phenprobamate
Phenylmercuric Borate	Pine Oil	Polacrilin
Polyacrylate Dispersion 30 Percent ***(Received)***	Polydextrose	Polydextrose Solution
Polyglycerol Esters of Fatty Acids	Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil (USP has 35)
Polyoxyl Stearate (USP has 40)	Polypropylene Oleate	Polyvinyl Acetate
Polyvinylacetal	Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone
Polypropylene Stearyl Ether	Polyvinylpyrrolidone Ethylcellulose	Polysorbate 65
Potassium Acid Tartrate	Potassium Alginate ***(Received)***	Potassium Bromate
Potassium Carbonate Solution	Potassium Dichloroisocyanurate	Potassium Gibberellate
Potassium Glycerophospate	Potasssium Iodate	Potassium Nitrite
Potassium Phosphate	Potassium Phosphate Tribasic	Potassium Polymetaphosphate
Potassium Pyrophosphate	Potassium Stearate	Potassium Sulfate
Potassium Sulfite	Potassium Tripolyphosphate	Propylene Glycol Diacetate
Propylene Glycol Mono- and Diesters	Propylene Glycol Monolaurate ***(Received)***	Propyl Propionate
Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil, Hydrogenated	Rapeseed Oil, Superglycerinated
Rice Bran Wax	Rosin	Silicone
Sodium Acid Pyrophosphate	Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic
Sodium Aluminum Phosphate Basic	Sodium Aspartate	Sodium Bisulfate
Sodium Bisulfite	Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan
Sodium Caseinate	Sodium Chlorate	Sodium Citrate, Dibasic
Sodium Citrate, Monobasic	Sodium Cyclamate	Sodium Dehydroacetate
Sodium Diacetate	Sodium Erythorbate	Sodium Ferric Pyrophosphate
Sodium Ferrocyanide	Sodium Hypophosphite	Sodium Laureth Sulfate
Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate
Sodium Magnesium Silicate	Sodium Malate	Sodium Metaphosphate, Insoluble
Sodium Metasilicate	Sodium Methylate	Sodium Polyphosphates Glassy
Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate
Sodium Sesquicarbonate	Sodium Sesquinoleate	Sodium Stearoyl Lactylate
Sodium Thiomalate	Sodium Trimetaphosphate	Sodium Trioleate
Sodium Tripolyphosphate	Soy Polysaccharides	Stannous Chloride
Stannous Tartrate	Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca
Stearalkonium Chloride	Stearyl Citrate	Stearyl Monoglyceridyl Citrate
Succinylated Monoglycerides	Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters
Sucrose Stearate	Sucrose Syrup	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tallow	Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetеareth-4 Phosphate
Trichloroethylene	Trimyristin	Trisidium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Gluten	Wheat Germ Oil	Whey

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2005 and 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

2005-2006 Calendar of Pharmacopeial Education Courses

Date	Name of Course	Location
2-Nov-05	Fundamentals of Dissolution—Lecture	USP Headquarters
3-Nov-05	Fundamentals of Dissolution—Laboratory	USP Headquarters
4-Nov-05	Fundamentals of Microbiological Testing	California State University—Fullerton
15-Nov-05	Basic Statistics and their Practical Applications to the *USP–NF*	North Carolina State University—Raleigh
7-Dec-05	Effectively Using the *USP–NF*—Session I	Brussels, Belgium
8-Dec-05	Effectively Using the *USP–NF*—Session II	Brussels, Belgium
14-Feb-06	Fundamentals of Dissolution—Lecture	USP Headquarters
15-Feb-06	Fundamentals of Dissolution—Laboratory	USP Headquarters
23-Feb-06	Effectively Using the *USP–NF*—Session I and Session II (one day)	North Carolina State University—Raleigh

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

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, with a copy to USP, 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
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NAKASHIMA Nobumasa
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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 an issue of *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 schedule provided below will repeat every year so that users will know what to expect and become familiar with the deadlines. 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.

Publication and Comment Schedule for *USP 29–NF 24*

Pharmacopeial Forum	Targeted Official Publication	Comment Deadline
PF 31(1) and *PF* 31(2)	*USP 29–NF 24*	May 15, 2005
PF 31(3)	*USP 29–NF 24 1st Supplement*	August 15, 2005
PF 31(4) and *PF* 31(5)	*USP 29–NF 24 2nd Supplement*	December 16, 2005
PF 31(6) and *PF* 32(1)	*USP 30–NF 25*	To be announced
PF 32(2) and *PF* 32(3)	*USP 30–NF 25 1st Supplement*	To be announced
PF 32(4) and *PF* 32(5)	*USP 30–NF 25 2nd Supplement*	To be announced
PF 32(6) and *PF* 33(1)	*USP 31–NF 26*	To be announced

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, 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
PF 31(6) [Nov.–Dec. 2005]	Nov. 2005	Not Applicable
6th IRA [published in *PF* 31(6)]	Nov. 2005	Dec. 1, 2005
PF 32(1) [Jan.–Feb. 2006]	Jan. 2006*	Not Applicable
1st IRA [published in *PF* 32(1)]	Jan. 2006*	Feb. 1, 2006*
1st Supplement	Feb. 2006*	Apr. 1, 2006*
PF 32(2) [Mar.–Apr. 2006]	Mar. 2006*	Not Applicable
2nd IRA [published in *PF* 32(2)]	Mar. 2006*	Apr. 1, 2006*
PF 32(3) [May–June 2006]	May 2006*	Not Applicable
3rd IRA [published in *PF* 32(3)]	May 2006*	June 1, 2006*
2nd Supplement	June 2006*	Aug. 1, 2006*
PF 32(4) [July–Aug. 2006]	July 2006*	Not Applicable
4th IRA [published in *PF* 32(4)]	July 2006*	Aug. 1, 2006*
PF 32(5) [Sept.–Oct. 2006]	Sept. 2006*	Not Applicable
5th IRA [published in *PF* 32(5)]	Sept. 2006*	Oct. 1, 2006*
PF 32(6) [Nov.–Dec. 2006]	Nov. 2006*	Not Applicable
6th IRA [published in *PF* 32(6)]	Nov. 2006*	Dec. 1, 2006*

*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 (*USP28*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 28*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 28–NF 23*. 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 28* and to *NF 23*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Eric B. Sheinin, Ph.D., *Chief Science Officer*

Official December 1, 2005 **Released November 1, 2005**

All inquiries and comments regarding *USP 28* text and *NF 23* 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 not available when the associated monograph was made official, have since become available. The respective official date of each *USP 28* or *NF 23* standard, test, or assay requiring the use of the following Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Ademetione Disulfate Tosylate RS (January 1, 2006)
USP Agnuside RS (November 1, 2005)
USP Asparagine Anhydrous RS (November 1, 2005)
USP Asparagine Monohydrate RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound A RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound B RS (November 1, 2005)
USP Bupropion Hydrochloride Related Compound C RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound F RS (January 1, 2006)
USP Casticin RS (November 1, 2005)
USP Ciclopirox RS (January 1, 2006)
USP Ciclopirox Related Compound A RS (January 1, 2006)
USP Ciclopirox Related Compound B RS (January 1, 2006)
USP Clopidogrel Bisulfate RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound A RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound B RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound C RS (March 1, 2006)
USP 2-Deoxy-D-glucose RS (November 1, 2005)
USP Desoaminylazithromycin RS (January 1, 2006)
USP Diethanolamine RS (November 1, 2005)
USP Eleutheroside B RS (January 1, 2006)
USP Eleutheroside E RS (January 1, 2006)
USP Fluvoxamine Maleate RS (November 1, 2005)
USP L-Fucose RS (November 1, 2005)
USP Galactitol RS (January 1, 2006)
USP Hydrastine RS (May 1, 2006)
USP Insulin Lispro RS (March 1, 2006)
USP Maltose Monohydrate RS (January 1, 2006)
USP Mefloquine Hydrochloride RS (May 1, 2006)
USP Mefloquine Related Compound A RS (May 1, 2006)
USP Monoethanolamine RS (November 1, 2005)
USP Norphenylephrine Hydrochloride RS (May 1, 2006)
USP Oleic Acid RS (November 1, 2005)
USP Phenylethyl Alcohol RS (November 1, 2005)
USP Polyoxyl 20 Cetostearyl Ether RS (March 1, 2006)
USP Polyoxyl 20 Stearyl Ether RS (March 1, 2006)
USP Prilocaine RS (January 1, 2006)
USP Prilocaine Related Compound A RS (January 1, 2006)
USP Propofol RS (January 1, 2006)
USP Propofol Related Compound A RS (January 1, 2006)
USP Propofol Related Compound B RS (January 1, 2006)
USP Propofol Related Compound C RS (January 1, 2006)
USP Propofol Resolution Mixture C RS (January 1, 2006)
USP Ramipril Related Compound D RS (November 1, 2005)
USP Residual Solvent Class 2—Hexane RS (November 1, 2005)
USP Residual Solvents Class 2—Mixture B RS (January 1, 2006)
USP Sodium Benzoate RS (January 1, 2006)
USP Stavudine RS (January 1, 2006)
USP Stavudine System Suitability Mixture RS (January 1, 2006)
USP Sulfaquinoxaline Related Compound A RS (January 1, 2006)
USP Sumatriptan Succinate Related Impurities RS (November 1, 2005)
USP Tiagabine Related Compound A RS (May 1, 2006)
USP Racemic Tiagabine Hydrochloride Mixture RS (May 1, 2006)
USP Tiagabine Hydrochloride RS (May 1, 2006)
USP Tagatose RS (January 1, 2006)
USP Thymol RS (November 1, 2005)
USP Tilmicosin RS (November 1, 2005)
USP Trenbolone CIII RS (November 1, 2005)
USP Trenbolone Acetate CIII RS (November 1, 2005)
USP Trolamine RS (November 1, 2005)

Unavailable First-Time Official Reference Standards

The official dates of any *USP 28* or *NF 23* 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. This listing was updated as of September 1, 2005.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Berberine Chloride RS
USP Budesonide RS
USP Cetrimonium Bromide RS
USP Copolymer Polypropylene RS
USP Cytosine RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluticasone Propionate Resolution Mixture RS
USP Fluticasone Propionate System Suitability Mixture RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Mecamylamine Related Compound A RS
USP Menotropins RS
USP Methyldopa-glucose Reaction Product RS
USP Miboleron RS
USP Narasin RS
USP Naratriptan Resolution Mixture RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Ondansetron RS
USP Paricalcitol Solution RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS

USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Maritime Pine Extract RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Propofol for System Suitability RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Ropivacaine Hydrochloride RS
USP Ropivacaine Related Compound A RS
USP Ropivacaine Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tinidazole Related Compound B RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

NOTICE OF OFFICIAL STATUS

Assay under _Vinorelbine Injection_ (_First Supplement_ to _USP 28–NF 23,_ page 3281 and the _Fifth Interim Revision Announcement_ to _USP 28–NF 23_ on page 1326 of _PF_ 31(5) [Sept.–Oct. 2005]).

USP is making the *Assay* test in the *Vinorelbine Injection* monograph official, thus removing the recent retroactive postponement of this test published in the *5th IRA.* This NOTICE OF OFFICIAL STATUS applies as of November 1, 2005.

The retroactive postponement was applied to allow USP to develop a lot of USP Vinorelbine Tartrate Reference Standard (RS) that is suitable for all official USP compendial applications. A new lot of USP Vinorelbine Tartrate RS has been developed, is suitable for both quantitative and qualitative testing purposes required by the *Vinorelbine Injection* monograph, and is currently available.

This notification is consistent with the *General Notices* section of *USP 28–NF 23* relating to USP Reference Standards, which states the following:

> The requirements for any new *USP* or *NF* standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the *USP* or *NF* standards, tests, or assays requiring their use are announced via *Supplements* or *Interim Revision Announcements.*

If you have any questions or concerns, please contact Lawrence Evans III, Ph.D., Scientist, DSD and Scientific Liaison to the Monograph Development: Ophthalmology, Oncology, and Dermatology Expert Committee (formerly Pharmaceutical Analysis 6 Expert Committee) (301-816-8389 or le@usp.org).

Interim Revision Announcement

Vinorelbine Injection

Change to read:

•**Assay**—

Phosphate buffer, Mobile phase, and *System suitability solution*—Proceed as directed in the test for *Related compounds* under *Vinorelbine Tartrate*.

Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about 0.10 mg of vinorelbine (base) per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode-array detector and a 3.9-mm × 15-cm column that contains packing L1. The column temperature is maintained at 40°. 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 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A; and the relative retention, α, between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.

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 vinorelbine peaks, using a diode-array detector. Calculate the quantity, in mg, of vinorelbine ($C_{45}H_{54}N_4O_8$) in each mL of the Injection taken by the formula:

$$C(L/D)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation; L* is the labeled quantity, in mg, of vinorelbine in each mL of Injection taken; D is the concentration, in mg per mL, of vinorelbine in the *Assay preparation;* and r_U and r_S are the peak responses at 267 nm obtained from the *Assay preparation* and the *Standard preparation,* respectively.•6

NOTICE OF POSTPONEMENT

⟨905⟩ *Uniformity of Dosage Units*

USP has **postponed the official date from April 1, 2006, until January 1, 2007,** for the revised, harmonized general chapter *Uniformity of Dosage Units* ⟨905⟩ that was published on pages 2505–2510 of *USP 28–NF 23.* The postponement is intended to provide additional time for the Pharmacopeial Discussion Group to evaluate comments received concerning this revision.

Comments were received regarding that portion of the unofficial, harmonized general chapter text that provides for the use of the *Weight Variation* test in place of the *Content Uniformity* test in cases where "the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data." The comments indicated that dosage unit uniformity should be independent of process validation data and product development data because these data may not always be available to regulatory agencies. The comments indicated further that the proposed wording would therefore require regulatory agencies and others that conduct dosage unit uniformity testing to obtain data from the sponsoring firm to determine whether to use a weight variation test or a content uniformity test in certain cases. Therefore, the proposed wording creates a private standard, because an analyst would need information outside that provided in the *USP–NF* to conduct the compendial test. The proposed standard would allow for different standards based on proprietary data held only by the drug sponsor.

Should you have any questions, please contact W. Larry Paul, Ph.D., Scientific Fellow, General Policies and Requirements Division (301-816-8331 or wlp@usp.org).

Change to read:

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

[NOTE—In this chapter, *unit* and *dosage unit* are synonymous.]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* (see *Table 1*). The test for *Content Uniformity* is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases. The test for *Content Uniformity* is required for those dosage forms described in *(C1)–(C6)* below:

NOTICE OF POSTPONEMENT (*continued*)

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg & ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules			WV	WV
Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

(C1) coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;
(C2) transdermal systems;
(C3) suspensions or emulsions or gels in unit-dose containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for external, cutaneous administration);
(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩;
(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for *Weight Variation* may be applied in the special situations stated in *(W2)* and *(W3)* below; and
(C6) suppositories.

The test for *Weight Variation* is applicable for the following dosage forms:

(W1) solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules;
(W2) solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive;
(W3) solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting *Content Uniformity* requirements.

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NOTICE OF POSTPONEMENT (*continued*)

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the *Weight Variation* test. Alternatively, products listed in item (W4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by *Weight Variation* instead of the *Content Uniformity* test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents ($\chi_1, \chi_2, \ldots, \chi_n$), expressed as a percentage of the label claim		
$\chi_1, \chi_2, \ldots, \chi_n$	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If $n = 10$, then $k =$	2.4
		If $n = 30$, then $k =$	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}\left(\chi_i - \overline{X}\right)^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$\frac{100s}{\overline{X}}$
M (case 1) to be applied when $T \leq 101.5$	Reference value	If $98.5\% \leq \overline{X} \leq 101.5\%$, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X} < 98.5\%$, then	$M = 98.5\%$ $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X} > 101.5\%$, then	$M = 101.5\%$ $(AV = \overline{X} - 101.5 + ks)$
M (case 2) to be applied when $T > 101.5$	Reference value	If $98.5 \leq \overline{X} \leq T$, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X} < 98.5\%$, then	$M = 98.5\%$ $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X} > T$, then	$M = T\%$ $(AV = \overline{X} - T + ks)$
Acceptance value *(AV)*			general formula: $\left\lvert M - \overline{X} \right\rvert + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		*L1* = 15.0 unless otherwise specified in the individual monograph/tbody>

NOTICE OF POSTPONEMENT (*continued*)

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of *M*	On the low side, no dosage unit result can be less than $(1 - L2*0.01)M$, while on the high side no dosage unit result can be greater than $(1 + L2*0.01)M$. (This is based on an *L2* value of 25.0.)	*L2* = 25.0 unless otherwise specified in the individual monograph
T	Target test sample amount at time of manufacture. For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, *T* is 100.0%, and for manufacturing purposes, *T* is the manufacturer's approved target test amount value at the time of manufacture.		

CONTENT UNIFORMITY

Select not less than 30 units, and proceed as follows for the dosage form designated. Where the amount of drug substance in a single dosage unit differs from that required in the *Assay,* adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the drug substances in the final solution is of the same order as that obtained in the *Assay* procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see *Titrimetry* ⟨541⟩); see also *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. If any such modifications are made in the *Assay* procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special *Procedure for content uniformity* is specified in the test for *Uniformity of dosage units* in the individual monograph, make any necessary correction of the results obtained as follows.

(1) Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the *Assay* in the individual monograph plus the amount required for the special *Procedure for content uniformity* in the monograph by finely powdering tablets or mixing the contents of capsules or oral solutions, suspensions, emulsions, gels, or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the drug substance, and use appropriate aliquot portions of this solution for the specified procedures.

(2) Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the *Assay,* and (b) using the special *Procedure for content uniformity* in the monograph.

(3) Calculate the weight of drug substance equivalent to 1 average dosage unit, by (a) using the results obtained by the *Assay* procedure, and by (b) using the results obtained by the special procedure.

(4) Calculate the correction factor, *F,* by the formula:

$$F = W/P,$$

in which *W* is the weight of drug substance equivalent to 1 average dosage unit obtained by the *Assay* procedure, and *P* is the weight of drug substance equivalent to 1 average dosage unit obtained by the special procedure. If

$$\frac{100|W - P|}{W}$$

is greater than 10, the use of a correction factor is not valid.

(5) The correction factor is to be applied only if *F* is not less than 1.030 nor greater than 1.100, or not less than 0.900 nor greater than 0.970. If *F* is between 0.970 and 1.030, no correction is required.

(6) If *F* lies between 1.030 and 1.100, or between 0.900 and 0.970, calculate the weight of drug substance in each dosage unit by multiplying each of the weights found using the special procedure by *F.*

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers, and Solids (including Sterile Solids) in Single-Unit Containers—Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity* in the individual monograph. Calculate the acceptance value as directed below.

For oral solutions, oral suspensions, oral emulsions, or oral gels in single-unit containers, conduct the *Assay* on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, or for highly viscous products, conduct the *Assay* on the amount of well-mixed material that is obtained by quantitatively removing the contents from an individual container, and express the results as the delivered dose.

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NOTICE OF POSTPONEMENT (*continued*)

Calculation of Acceptance Value—Calculate the acceptance value by the formula:

$$\left|M - \overline{X}\right| + ks,$$

in which the terms are as defined in *Table 2*.

Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units—[NOTE—Acceptance value calculations are not required for these dosage forms.] Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity.*

WEIGHT VARIATION

Select not less than 30 dosage units, and proceed as follows for the dosage form designated. The result of the *Assay,* obtained as directed in the individual monograph, is designated as result *A,* expressed as % of label claim (see *Calculation of the Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. [NOTE—Specimens other than these test units may be drawn from the same batch for assay determinations.]

Uncoated or Film-Coated Tablets—Accurately weigh 10 tablets individually. Calculate the drug substance content, expressed as % of label claim, of each tablet from the weight of the individual tablet and the result of the *Assay.* Calculate the acceptance value.

Hard Capsules—Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Calculate the drug substance content, expressed as % of label claim, of each capsule from the net weight of the individual capsule content and the result of the *Assay.* Calculate the acceptance value.

Soft Capsules—Accurately weigh 10 intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content, expressed as % of label claim, in each capsule from the net weight of product removed from the individual capsules and the result of the *Assay.* Calculate the acceptance value.

Solids (Including Sterile Solids) in Single-Unit Containers—Proceed as directed for *Hard Capsules,* treating each unit as described therein. Calculate the acceptance value.

Oral Solutions Packaged in Single-Unit Containers—Accurately weigh the amount of liquid that drains in not more than 5 seconds from each of 10 individual containers. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content, expressed as % of label claim, in the liquid drained from each unit from the net weight of the individual container content and the result of the *Assay.* Calculate the acceptance value.

Calculation of Acceptance Value—Calculate the acceptance value as shown in *Content Uniformity,* except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$	=	individual estimated contents of the units tested, where $\chi_i = w_i \times A / \overline{W}$,
$w_1, w_2, \ldots, w_n$	=	individual weights of the units tested,
A	=	content of drug substance (% of label claim) determined as described in the *Assay,* and
$\overline{W}$	=	mean of individual weights $(w_1, w_2, \ldots, w_n)$.

Solutions for Inhalation Packaged in Glass or Plastic Ampuls and Intended for Use in Nebulizers—[NOTE—Acceptance value calculations are not required for these dosage forms.] Accurately weigh 10 containers individually, taking care to preserve the identity of each container. Remove the contents of each container by a suitable means. Accurately weigh the emptied containers individually, and calculate for each container the net weight of its contents by subtracting the weight of the container from the respective gross weight. From the results of the *Assay,* obtained as directed in the individual monograph, calculate the drug substance content, expressed as % of label claim, in each of the containers.

CRITERIA

Apply the following criteria, unless otherwise specified in the individual monograph.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers, and Solids (Including Sterile Solids) in Single-Unit Containers—The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to *L1*%. If the acceptance value is greater than *L1*%, test the next 20 units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to *L1*%, and no individual content of any dosage unit is less than $(1 - L2*0.01)M$ nor more than $(1 + L2*0.01)M$ as specified in the *Calculation of Acceptance Value* under *Content Uniformity* or under *Weight Variation.* Unless otherwise specified in the individual monograph, *L1* is 15.0 and *L2* is 25.0.

Suppositories—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the *Content Uniformity* method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.

If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.

NOTICE OF POSTPONEMENT (*continued*)

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*
(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

Transdermal Systems and Inhalations Packaged in Premetered Dosage Units—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in not less than 9 of the 10 dosage units as determined from the *Content Uniformity* method (or, in the case of solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, from either the *Content Uniformity* or the *Weight Variation* method) lies within the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 10 dosage units is less than or equal to 6.0%.

If 2 or 3 dosage units are outside the range of 85.0% to 115.0% of label claim, but not outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 30 dosage units does not exceed 7.8%.

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*
(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

•(Official January 1, 2007)•6

Interim Revision Announcement

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

⟨1⟩ INJECTIONS

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. •For containers with a nominal volume of 2 mL or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement, pro-

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vided that a separate, dry syringe assembly is used for each container.•6 The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. •Cool to between 20 and 25°•6 before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

•(Postponed indefinitely)•5

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.

Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

ERRATA

Following is a list of errata and corrections to *USP 28–NF 23*. The page number indicates where the item is found in *USP 28–NF 23*. 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
269	*Bisoprolol Fumarate Tablets*	*Thin-layer chromatographic identification test* ⟨201⟩	Line 2 under *Developing solvent system:* Change "ammonia TS" to: ammonia TS, stronger
1647	*Propofol*	*Limit of propofol related compound A*	Line 1 under *Procedure:* Change "Separately inject equal volumes (about 20 mL)" to: Separately inject equal volumes (about 20 µL)
2450	⟨788⟩ *Particulate Matter in Injections*	*Instrument Standardization, Sensor Resolution*	Equation under *Manual Method:* Change $100\left[\left(\sqrt{S_O^{\,2} - S_S^{\,2}}\right) ID\right],$ to: $100\left(\sqrt{S_O^{\,2} - S_S^{\,2}/D}\right)$
2509	⟨905⟩ *Uniformity of Dosage Units*	*Criteria*	Under *Suppositories, Limit B*, re-insert text to the list. List should read as follows: (1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A*. (2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100". (3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".
Supplement 2			
3476	*Diclofenac Sodium Delayed-Release Tablets*	*Drug Release, Method B* ⟨724⟩, *Acid Stage*	Line 12 under *Procedure:* Change "Transfer 3.0 mL of this solution to a second 100-mL volumetric flask" to: Transfer 2.0 mL of this solution to a second 100-mL volumetric flask

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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:
>
> (DSN: L. Evans) 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, as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 28–NF 23* (*IRA*);

▲new text▲*USP29*

if slated for *USP 29–NF 24* or for *USP 30–NF 25*; and

■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*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP29* and ▲*NF24* indicate that the revisions are proposed for *USP 29* and *NF 24*, 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.

MONOGRAPHS (USP)

BRIEFING

Amitriptyline Hydrochloride, *USP 28* page 135. It is proposed to replace the UV *Identification* test with HPLC retention time. It is proposed to delete the test for *Chromatographic purity,* using TLC, and add a test for *Related compounds,* using HPLC. It is proposed to replace the titrimetric method in the *Assay* with HPLC; it is also proposed to add the associated *USP Reference standards* used in the *Assay.* The HPLC method uses a Phenomenex brand Luna C8 column. The retention time of amitriptyline is about 16.5 minutes.

(MD-PP: R. Ravichandran) RTS—42021-1

Change to read:

USP Reference standards ⟨11⟩—*USP Amitriptyline Hydrochloride RS.*

▲*USP Amitriptyline Related Compound A RS. USP Amitriptyline Related Compound B RS. USP Cyclobenzaprine Hydrochloride RS. USP Nortriptyline Hydrochloride RS.*▲*USP30*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

~~**B:** *Ultraviolet Absorption* ⟨197U⟩—~~

~~*Solution:* 10 µg per mL.~~

~~*Medium:* methanol.~~

~~Absorptivities at 239 nm, calculated on the dried basis, do not differ by more than 3.0%.~~

▲**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.*▲*USP30*

C: It responds to the tests for *Chloride* ⟨191⟩.

Delete the following:

▲~~**Chromatographic purity**—~~

~~*Standard solutions*—Dissolve USP Amitriptyline Hydrochloride RS in methanol, and mix to obtain a solution having a known concentration of 0.8 mg per mL. Quantitatively dilute this solution with methanol to obtain *Standard solutions*, designated below by letter, having the following compositions:~~

~~Standard Preparation~~	~~Dilution~~	~~Concentration (µg RS per mL)~~	~~Percentage (%, for comparison with test specimen)~~
~~*A*~~	~~(1 in 2)~~	~~400~~	~~1.0~~
~~*B*~~	~~(1 in 4)~~	~~200~~	~~0.5~~
~~*C*~~	~~(1 in 5)~~	~~160~~	~~0.4~~
~~*D*~~	~~(1 in 10)~~	~~80~~	~~0.2~~
~~*E*~~	~~(1 in 20)~~	~~40~~	~~0.1~~

~~*Test solution*—Dissolve an accurately weighed quantity of Amitriptyline Hydrochloride in methanol to obtain a solution containing 40 mg per mL.~~

~~*Procedure*—Apply separately 10 µL of the *Test solution* and 10 µL of each *Standard solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the applications to dry, position the plate in a chromatographic chamber, and develop the chromatograms in a solvent system consisting of a mixture of chloroform, methanol, and ammonium hydroxide (135 : 15 : 1) 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. Examine the plate under short wavelength UV light. 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*. [NOTE—Disregard any spots observed at the origins of the chromatograms.] No secondary spot from the chromatogram of the *Test solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.5%), and the sum of the intensities of all secondary spots obtained from the *Test solution* corresponds to not more than 1.0%. Disregard any spot in the chromatogram of the *Test solution* that is smaller or less intense than the principal spot obtained from *Standard solution E* (0.1%).~~▲*USP30*

Add the following:

▲**Related compounds**—

Diluted phosphoric acid, Buffer, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Use the *System suitability preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation*.

In-Process Revision

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentages of individual amitriptyline related compounds in the portion of Amitriptyline Hydrochloride taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U is the individual peak response for each amitriptyline related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* C_S is the concentration, in mg per mL, of each of the amitriptyline related compounds in the *Standard solution;* and C_T is the concentration, in mg per mL, of amitriptyline hydrochloride in the *Test solution*. The related compound requirements are listed in *Table 1.*

Table 1

Related Compound	Relative Retention Time	Limit (%)
Amitriptyline related compound A	0.35	0.05
Amitriptyline related compound B	0.52	0.15
Nortriptyline hydrochloride	0.60	0.15
Cyclobenzaprine hydrochloride	0.76	0.15
Amitriptyline hydrochloride	1.0	—
Unknown	—	0.10 each
Total known and unknown	—	1.0

[NOTE—Discard any peak with a relative retention time of less than 0.22. Use the response of the amitriptyline hydrochloride peak obtained from the *Standard solution* and the concentration of amitriptyline hydrochloride in the *Standard solution* to calculate the percentage of unknown individual impurities.]▲*USP30*

Change to read:

Assay— ~~Dissolve about 1 g of Amitriptyline Hydrochloride, accurately weighed, in 30 mL of glacial acetic acid, warming slightly if necessary to effect solution. Cool, add 10 mL of mercuric acetate TS, then add crystal violet TS, and titrate with 0.1 N perchloric acid VS to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 31.39 mg of $C_{20}H_{23}N \cdot HCl$.~~

▲*Diluted phosphoric acid*—Prepare a mixture of phosphoric acid and water (1 : 10), and mix well.

Buffer—Dissolve 1.42 g of dibasic sodium phosphate (Na_2HPO_4) in 1 L of water, and adjust with *Diluted phosphoric acid* to a pH of 7.7.

Mobile phase—Prepare a mixture of filtered and degassed methanol and *Buffer* (7 : 3).

Assay stock preparation—Dissolve an accurately weighed amount of Amitriptyline Hydrochloride in *Mobile phase* to obtain a solution having a known concentration of about 1 mg per mL of amitriptyline hydrochloride.

Standard preparation—Dissolve an accurately weighed amount of USP Amitriptyline Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 0.2 mg per mL of amitriptyline hydrochloride.

Assay preparation—Dilute the *Assay stock preparation* with *Mobile phase* (1 : 5).

Stock solution A—Dissolve an accurately weighed amount of USP Amitriptyline Related Compound A RS in methanol to obtain a solution having a known concentration of about 1 mg per mL of amitriptyline related compound A.

Stock solution B—Dissolve accurately weighed amounts of USP Amitriptyline Hydrochloride RS, USP Amitriptyline Related Compound B RS, USP Cyclobenzaprine Hydro-

chloride RS, and USP Nortriptyline Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.4 mg per mL of amitriptyline hydrochloride and about 0.6 mg per mL each of amitriptyline related compound B, cyclobenzaprine hydrochloride, and nortriptyline hydrochloride.

System suitability preparation—Dilute suitable volumes of *Stock solution A, Stock solution B,* and the *Standard preparation* with *Mobile phase* to obtain a solution having 1 µg per mL of amitriptyline hydrochloride, 0.5 µg per mL of amitriptyline related compound A, and 1.5 µg per mL each of amitriptyline related compound B, cyclobenzaprine hydrochloride, and nortriptyline hydrochloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 45°. Chromatograph the *System suitability preparation,* and record the peak areas as directed for *Procedure:* the approximate relative retention times for related compounds are given in *Table 1;* and the resolution, *R,* between amitriptyline related compound B and nortriptyline is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative standard deviation for amitriptyline 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 for about 40 minutes, and measure the responses for the major peaks. Calculate the percentage of $C_{20}H_{23}N \cdot HCl$ in the portion of Amitriptyline Hydrochloride taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of the *Standard preparation* and the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Calcium Lactate, *USP 28* page 329. It is proposed to replace *Identification* test *B* with a test for *Identification* based on infrared spectroscopy. The new test will require the use of a new USP Reference Standard that is also being proposed.

(DSN: L. Evans) RTS—42823-1

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Calcium Lactate RS.*▲*USP30*

Change to read:

Identification—

A: A solution (1 in 20) responds to the tests for *Calcium* ⟨191⟩.

B: ~~To 10 mg add 1 mL of sulfuric acid, and heat for 2 minutes in a water bath maintained at a temperature of 85°. Cool the solution to room temperature, add about 10 mg of 4-phenylphenol crystals, swirl, and allow to stand for about 20 minutes: a violet color develops that deepens with the passage of time.~~

▲*Infrared Absorption* ⟨197K⟩.▲*USP30*

In-Process Revision

BRIEFING

Calcium Lactate Tablets, *USP 28* page 329 and page 81 of *PF* 30(1) [Jan.–Feb. 2004]. Editorial changes have been made to *Identification* test *B* to remove the reference to the monograph for *Calcium Lactate.*

(DSN: L. Evans) RTS—42823-2

Change to read:

Identification—

A: A filtered solution of Tablets, equivalent to calcium lactate solution (1 in 20), responds to the tests for *Calcium* ⟨191⟩.

B: A filtered solution of Tablets, equivalent to calcium lactate solution (1 in 20), responds to ~~*Identification* test *B* under *Calcium Lactate*, 1 drop of the solution being used.~~

▲the tests for *Lactate* ⟨191⟩.▲*USP30*

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~

■■1S (*USP29*)
⟨711⟩—
Medium: water; 500 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure—

■Proceed as directed for *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.■1S (*USP29*)
Determine the amount of $C_6H_{10}CaO_6 \cdot 5H_2O$ dissolved, employing the procedure set forth in the *Assay,* making any necessary modifications.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_6H_{10}CaO_6 \cdot 5H_2O$ is dissolved in 45 minutes:

■the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q,* is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

■1S (*USP29*)

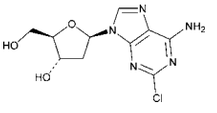
BRIEFING

Cladribine, page 395 of *PF* 31(2) [Mar.–Apr. 2005]. On the basis of comments received, it is proposed to revise the specification in the test for *Specific rotation* by adding a significant figure to both the upper and the lower limits. It is also proposed to revise the test for *Related compounds* by adding a significant figure to each of the limits shown in *Table 1.* In the *Limit of residual solvents* test, it is proposed to revise the limit of methanol to reflect the limits of Class 2 solvents as given in the general chapter *Organic Volatile Impurities* ⟨467⟩.

(MD-OOD: L. Evans) RTS—43097-1

Add the following:

■Cladribine



$C_{10}H_{12}ClN_5O_3$ 285.69

Adenosine, 2-chloro-2′-deoxy-.

2-Chloro-2′-deoxyadenosine [*4291-63-8*].

In-Process Revision

» Cladribine contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}ClN_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and protect from light. Store between 2° and 8°.

USP Reference standards ⟨11⟩—*USP Cladribine RS. USP Cladribine 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.*

Change to read:

Specific rotation ⟨781S⟩**:** between ~~–17° and –21°~~ ▲–17.0° and –21.0°.▲*USP30*

Test solution: 10 mg per mL, in dimethylformamide.

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Change to read:

Related compounds—

Buffer, Diluent, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; and the tailing factor is not more than 2.0.

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 Cladribine taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of each individual impurity, and r_s is the sum of the responses of all the peaks. Refer to *Table 1* for the impurity limits.

Table 1

Name	Relative Retention Time	Limit (%)
2,6-Diaminopurine-2′-deoxyriboside	about 0.41	~~0.2~~ ▲0.20▲*USP30*
2′-Deoxyadenosine	about 0.47	~~0.2~~▲0.20▲*USP30*
2-Chloroadenine	about 0.60	~~0.2~~▲0.20▲*USP30*
2-Methoxy-2′-deoxyadenosine (cladribine related compound A)	about 0.91	~~0.2~~▲0.20▲*USP30*
Any ~~other individual~~ ▲individual unspecified▲*USP30* impurity	—	~~0.1~~▲0.10▲*USP30*
Total impurities	—	1.0

In-Process Revision

Change to read:

Limit of residual solvents—

Standard solution—Transfer 15 µL of methanol and 24 µL of alcohol to a 100-mL volumetric flask containing 80 mL of water, dilute with water to volume, and mix. Transfer 3 mL of the solution to a 20-mL headspace vial. The concentrations of methanol and alcohol are 119 µg per mL and 198 µg per mL, respectively.

Test solution—In a 20-mL headspace vial, dissolve 200 mg of Cladribine, accurately weighed, in 5 mL of water.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame-ionization detector and contains a 0.53-mm × 30-m column coated with a 5-µm film of liquid phase G16. The carrier gas is nitrogen, flowing at a rate of 4 mL per minute. The split ratio is 5 : 1. Vials containing the *Standard solution* and the *Test solution* are equilibrated for 10 minutes at 80° in the headspace sampler. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 80° for 6 minutes, then it is increased at a rate of 25° per minute to 240° and held at 240° for 20 minutes. The injection port temperature is maintained at 250°, and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between alcohol and methanol is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10.0% for each of the two solvents.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspaces of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration, in ppm, of each residual solvent in the portion of Cladribine taken by the formula:

$$5000(C/W)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of the respective individual solvent in the *Standard solution; W* is the quantity, in mg, of Cladribine 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 5000 ppm of alcohol is found, and not more than ~~450~~ ▲3000▲*USP30* ppm of methanol is found.

Assay—

Buffer—Dissolve 9.96 g of triethylamine phosphate, accurately weighed, in 500 mL of water, and add an additional 500 mL of water. Adjust with potassium hydroxide to a pH of 6.1.

Diluent—Prepare a mixture of water and methanol (90 : 10).

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and methanol (78 : 22). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Cladribine RS and USP Cladribine Related Compound A RS in *Diluent* to obtain known concentrations of about 2.0 mg per mL each.

Standard preparation—Dissolve an accurately weighed quantity of USP Cladribine RS in *Diluent* to obtain a concentration of 0.5 mg per mL.

Assay preparation—Transfer about 25 mg of Cladribine, accurately weighed, to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 4.6-mm × 15-cm column that contains packing

L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; the tailing factor for the cladribine peak in the *System suitability solution* is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* 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 $C_{10}H_{12}ClN_5O_3$ in the portion of Cladribine taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cladribine 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 *(USP29)*

BRIEFING

Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution, *USP 28* page 670, and page 3481 of the *Second Supplement*; **Diphenoxylate Hydrochloride and Atropine Sulfate Tablets**, *USP 28* page 671. A single HPLC *Assay* method, which allows determination of both components, is proposed for inclusion into these dosage form monographs. It will replace two separate HPLC assay methods in the monograph for Tablets, and a potentiometric titration and a tedious GC procedure in the monograph for Oral Solution. The liquid chromatographic procedure is based on analyses performed with the Spherisorb CN brand of L10 column. The typical retention times for atropine and diphenoxylate are about 5.5 and 15 minutes, respectively. It is also proposed to replace the *Identification* test for these monographs with HPLC retention time agreement of the major peaks in the *Assay preparation* and the *Standard preparation*.

(MD-GRE: E. Gonikberg) RTS—42094-1

Change to read:

Identification—~~Transfer a volume of Oral Solution, equivalent to about 100 mg of diphenoxylate hydrochloride, to a separator, add 1 mL of 3 N hydrochloric acid and sufficient water to make about 100 mL, and extract with five 25-mL portions of a mixture of chloroform and isopropyl alcohol (9 : 1). After each extraction transfer the bottom chloroform layer to a second separator, passing each portion through a sintered glass filter. Wash the combined chloroform solutions with two 25-mL portions of water, discard the washings, and evaporate the chloroform on a steam bath to dryness. To the residue add 10 mL of ether previously saturated with hydrochloric acid, carefully evaporate to dryness, then add a second portion of the acid-saturated ether, and again evaporate to dryness. Make a slurry of the residue with *n*-hexane, allow the solids to settle, and carefully decant the supernatant. Dry the solids at 105° for 1 hour: the diphenoxylate hydrochloride so obtained meets the requirements for *Identification* tests *A* and *B* under *Diphenoxylate Hydrochloride.*~~

▲The retention times of two major peaks in the chromatogram of the *Assay preparation* correspond to the atropine and diphenoxylate peaks in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*▲*USP30*

Delete the following:

▲~~**Assay for diphenoxylate hydrochloride**—Transfer an accurately measured volume of Oral Solution, equivalent to about 100 mg of diphenoxylate hydrochloride, to a separator, add 4 mL of 3 N hydrochloric acid, and extract with six 30-mL portions of chloroform. Wash the combined chloroform extracts with 25 mL of water, and discard the washing. Transfer the chloroform to a beaker, and evaporate nearly to dryness. Add 100 mL of glacial acetic acid and 4 mL of mercuric acetate TS to the beaker, and titrate with 0.05 N perchloric acid in dioxane VS, determining the endpoint potentiometrically. Each mL of 0.05 N perchloric acid is equivalent to 24.45 mg of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_5 \cdot HCl$).~~▲*USP30*

Delete the following:

▲~~**Assay for atropine sulfate**—~~

~~*pH 2.8 Buffer*—Dissolve 1.9 g of aminoacetic acid and 1.5 g of sodium chloride in 250 mL of water. Adjust by the gradual addition of about 85 mL of 0.1 N hydrochloric acid to a pH of 2.8.~~

~~*Internal standard solution*—Transfer about 20 mg of homatropine hydrobromide to a 200-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

~~*Standard preparation*—Transfer about 25 mg of USP Atropine Sulfate RS, accurately weighed, to a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Pipet 2 mL of the resulting solution into a 125-mL separator containing about 50 mL of water. Add 2.0 mL of *Internal standard solution,* 10.0 mL of *pH 2.8 Buffer,* and 25 mL of water-saturated methylene chloride. Insert the stopper, shake for 2 minutes, and allow the layers to sep-~~

~~arate. Discard the lower, organic layer. Repeat the extraction four times, using 25-mL portions of water-saturated methylene chloride each time, allowing the layers to separate and discarding the organic layer each time. To the remaining aqueous layer add 3 mL of 0.1 N sodium hydroxide, and shake briefly. Using a pH meter, adjust the solution to a pH of 9.0 ± 0.3. Immediately add 10 mL of water-saturated methylene chloride, insert the stopper, and shake. Transfer the lower, organic layer to a 50-mL container. Repeat the extraction twice more with 10-mL portions of water-saturated methylene chloride, combining the organic extracts. Under a stream of nitrogen, evaporate the organic extracts to dryness. Dissolve the residue in 0.1 mL of methylene chloride.~~

~~*Assay preparation*—Transfer an accurately measured volume of Oral Solution, equivalent to about 250 µg of atropine sulfate, to a 125-mL separator. Proceed as directed for *Standard preparation,* beginning with "Add 2.0 mL of *Internal standard solution*."~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 1.2-m glass column that contains 3% phase G3 on support S1. The column is maintained at a temperature of 230°, and the injection port and detector temperatures are maintained at 250°. Helium is used as the carrier gas at a rate of 40 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between atropine and the internal standard is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.5%.~~

~~*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 µg, of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O]$ in each mL of the Oral Solution taken by the formula:~~

~~$$2(694.85/676.83)(C/V)(R_U/R_S),$$~~

~~in which 694.85 and 676.83 are the molecular weights of atropine sulfate monohydrate and anhydrous atropine sulfate, respectively; *C* is the concentration, in µg per mL, of USP Atropine Sulfate RS (corrected to the monohydrate) in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and R_U and R_S are the peak response ratios of atropine to the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~ ▲*USP30*

Add the following:

▲Assay—

Solution A—Transfer 192 mg of sodium 1-pentanesulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of water and 1.0 mL of phosphoric acid, and mix.

Solution B—Transfer 192 mg of sodium 1-pentanesulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of acetonitrile, 1.0 mL of phosphoric acid, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution B* and *Solution A* (66 : 34). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Atropine stock preparation—Dissolve an accurately weighed quantity of USP Atropine Sulfate RS in dehydrated alcohol, and dilute quantitatively, and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of about 0.04 mg per mL.

Standard preparation—Transfer about 20 mg of USP Diphenoxylate Hydrochloride RS to a 200-mL volumetric flask, add about 100 mL of dehydrated alcohol, and sonicate to dissolve. Accurately add 5.0 mL of *Atropine stock preparation* and 34 mL of water, and mix. Allow the solution to reach room temperature, and then dilute with dehydrated alcohol to volume. This solution contains about 0.1 mg of diphenoxylate hydrochloride and about 0.001 mg of atropine sulfate per mL.

Assay preparation—Transfer an accurately measured volume of the Oral Solution, equivalent to about 2.5 mg of diphenoxylate hydrochloride, based on the label claim, to a 25-mL volumetric flask, wash inside of the pipet with small portions of dehydrated alcohol, add the washings to the flask, dilute with dehydrated alcohol to volume, and mix. Pass a portion of the solution obtained through a 0.45-µm PTFE filter, discarding the first few mL, and use the clear 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 5-µm packing L10. The flow rate is about 1.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for atropine and 1.0 for diphenoxylate; the resolution, *R,* between atropine and diphenoxylate

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is not less than 5.0; the tailing factor is not more than 2.5 for diphenoxylate and not more than 1.5 for atropine; and the relative standard deviation for replicate injections is not more than 2.0% for diphenoxylate and not more than 5.0% for atropine.

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 diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$) in the portion of Oral Solution taken by the formula:

$$25C_D(r_U/r_S)$$

in which 25 is the volume, in mL, of the *Assay preparation;* C_D is the concentration, in mg per mL, of USP Diphenoxylate Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the diphenoxylate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Calculate the quantity, in mg, of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O]$ in the portion of Oral Solution taken by the formula:

$$(694.83/676.83)(25)C_A(r_U/r_S)$$

in which 694.83 and 676.83 are the molecular weights of atropine sulfate monohydrate and anhydrous atropine sulfate, respectively; 25 is the volume, in mL, of the *Assay preparation;* C_A is the concentration, in mg per mL, of USP Atropine Sulfate RS in the *Standard preparation;* and r_U and r_S are the atropine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets, *USP 28* page 671—See briefing under *Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution*.

(MD-GRE: E. Gonikberg) RTS—42094-2

Change to read:

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 for diphenoxylate hydrochloride.*~~

~~**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 for atropine sulfate.*~~

▲The retention times of two major peaks in the chromatogram of the *Assay preparation* correspond to the atropine and diphenoxylate peaks in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*▲*USP30*

Delete the following:

▲~~**Assay for diphenoxylate hydrochloride—**~~

~~*pH 2.7 Triethylamine phosphate buffer*—Transfer approximately 18 mL of triethylamine to a 2000-mL volumetric flask containing about 1000 mL of water, and mix. Add about 11.4 mL of phosphoric acid, mix, and dilute with water to volume.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of acetonitrile and *pH 2.7 Triethylamine phosphate buffer* (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Diphenoxylate Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.25 mg per mL.~~

~~*Assay preparation*—Transfer an accurately counted number of Tablets, equivalent to about 25 mg of diphenoxylate hydrochloride, to a 100-mL volumetric flask, add *Mobile phase*, and shake by mechanical means for about 30 minutes until the Tablets have disintegrated completely. 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 × 15-cm column that contains packing L7. 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 diphenoxylate hydrochloride 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~~

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~~for the major peaks. Calculate the quantity, in mg, of diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_3 \cdot HCl$) in the portion of Tablets taken by the formula:~~

~~$$(L/D)C(r_U/r_S),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Diphenoxylate Hydrochloride RS in the *Standard preparation*; *L* is the labeled amount, in mg, of diphenoxylate hydrochloride in each Tablet; *D* is the concentration, in mg per mL, of diphenoxylate hydrochloride in the *Assay preparation*; and r_U and r_S are the peak responses for diphenoxylate obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~ ▲*USP30*

Delete the following:

▲~~**Assay for atropine sulfate**~~

~~*pH 2.7 Triethylamine phosphate buffer*—Prepare as directed in the *Assay for diphenoxylate hydrochloride*.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *pH 2.7 Triethylamine phosphate buffer*, methanol, and acetonitrile (78 : 18 : 4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Atropine Sulfate RS in *Mobile phase*, and dilute quantitatively and stepwise with *Mobile phase* to obtain a solution having a known concentration of about 5 µg per mL.~~

~~*Assay preparation*—Transfer an accurately counted number of Tablets, equivalent to about 0.5 mg of atropine sulfate, to a 100-mL volumetric flask, add *Mobile phase*, and shake by mechanical means for about 30 minutes until the Tablets have disintegrated completely. Dilute with *Mobile phase* to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 206-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the tailing factor for the atropine peak 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 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 atropine sulfate [$(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$] in the portion of Tablets taken by the formula:~~

~~$$(694.85/676.83)(L/D)C(r_U/r_S),$$~~

~~in which 694.85 and 676.83 are the molecular weights of atropine sulfate monohydrate and anhydrous atropine sulfate, respectively; *C* is the concentration, in µg per mL, of USP Atropine Sulfate RS in the *Standard preparation*; *L* is the labeled amount, in mg, of atropine sulfate in each Tablet; *D* is the concentration, in µg per mL, of atropine sulfate 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 for atropine obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~ ▲*USP30*

Add the following:

▲**Assay**—

Diluent—Use a mixture of acetonitrile and water (1 : 1).

Solution A—Transfer 192 mg of sodium 1-pentanesulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of water and 1.0 mL of phosphoric acid, and mix.

Solution B—Transfer 192 mg of sodium 1-pentanesulfonate monohydrate to a suitable container, add 200 mL of water, and sonicate to dissolve. Add 800 mL of acetonitrile and 1.0 mL of phosphoric acid, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution B* and *Solution A* (66 : 34). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Atropine stock preparation—Dissolve an accurately weighed quantity of USP Atropine Sulfate RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.

Standard preparation—Transfer about 20 mg of USP Diphenoxylate Hydrochloride RS to a 200-mL volumetric flask, add about 100 mL of *Diluent,* and sonicate to dissolve. Accurately add 5.0 mL of *Atropine stock preparation,* and mix. Allow the solution to reach room temperature, and then dilute with *Diluent* to volume. This solution contains about 0.1 mg of diphenoxylate hydrochloride and about 0.001 mg of atropine sulfate per mL.

Assay preparation—Transfer an accurately counted number of Tablets, equivalent to about 25 mg of diphenoxylate hydrochloride, based on the label claim, to a 250-mL volumetric flask, add approximately 100 mL of *Diluent,* and

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shake by mechanical means for at least 15 minutes or until the Tablets are completely disintegrated. Sonicate for an additional 15 minutes, allow the solution to reach room temperature, dilute with *Diluent* to volume, and mix. Pass a portion of the solution obtained through a 0.45-µm PTFE filter, discarding the first few mL, and use the clear 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 5-µm packing L10. The flow rate is about 1.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for atropine and 1.0 for diphenoxylate; the resolution, *R,* between atropine and diphenoxylate is not less than 5.0; the tailing factor is not more than 2.5 for diphenoxylate and not more than 1.5 for atropine; and the relative standard deviation for replicate injections is not more than 2.0% for diphenoxylate and not more than 5.0% for atropine.

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 diphenoxylate hydrochloride ($C_{30}H_{32}N_2O_2 \cdot HCl$) in the portion of Tablets taken by the formula:

$$250C_D(r_U/r_S)$$

in which 250 is the volume, in mL, of the *Assay preparation;* C_D is the concentration, in mg per mL, of USP Diphenoxylate Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the diphenoxylate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Calculate the quantity, in mg, of atropine sulfate $[(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O]$ in the portion of the Tablets taken by the formula:

$$(694.83/676.83)(250)C_A(r_U/r_S)$$

in which 694.83 and 676.83 are the molecular weights of atropine sulfate monohydrate and anhydrous atropine sulfate, respectively; 250 is the volume, in mL, of the *Assay preparation;* C_A is the concentration, in mg per mL, of USP Atropine Sulfate RS in the *Standard preparation;* and r_U and r_S are the atropine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Diphtheria Toxin for Schick Test, *USP 28* page 672; **Hepatitis B Virus Vaccine Inactivated,** *USP 28* page 943; **Rubella and Mumps Virus Vaccine Live,** *USP 28* page 1743; **Schick Test Control,** *USP 28* page 1756. Because these vaccines and reagents are no longer manufactured and marketed, it is proposed to remove their monographs from the *USP–NF.*

(BBVV: T. Morris) RTS—42382-1

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Delete the following:

▲~~Diphtheria Toxin for Schick Test~~

~~» Diphtheria Toxin for Schick Test conforms to the regulations of the FDA concerning biologics (650.1 to 650.7) (see *Biologics* ⟨1041⟩). It is a sterile solution of the diluted, standardized toxic products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) of which the parent toxin contains not less than 400 MLD (minimum lethal doses) per mL or 400,000 MRD (minimum skin reaction doses) per~~

~~mL in guinea pigs. Its potency is determined in terms of the U.S. Standard Diphtheria Toxin for Schick Test, tested in guinea pigs.~~

~~**Packaging and storage**—Preserve at a temperature between 2° and 8°.~~

~~**Expiration date**—The expiration date is not later than 1 year after date of issue from manufacturer's cold storage (5°, 1 year).~~ ▲*USP30*

BRIEFING

Ensulizole, *USP 28* page 735, page 3221 of the *First Supplement,* and page 1363 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to correct the formula for the *Assay* calculation.

(MD-AA: B. Davani; BPC: M. Marques) RTS—43201-1

Change to read:

USP Reference standards ⟨11⟩—~~*USP Ensulizole RS*~~

■*USP Phenylbenzimidazole Sulfonic Acid RS.*■2S (*USP29*)

Change to read:

Assay—Transfer about 1200 mg of Ensulizole, accurately weighed, to a 300-mL iodine flask, and dissolve by stirring in 25 mL of 0.5 N sodium hydroxide. Add phenolphthalein TS, and titrate the excess with 0.5 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 137.15 mg of $C_{13}H_{10}N_2O_3S$. ■Calculate the percentage of $C_{13}H_{10}N_2O_3S$ in the portion of Ensulizole taken by the formula:

~~$$\frac{[(V_{NaOH} \times T_{NaOH}) - (V_{HCl} \times T_{HCl})] \times 0.5 \times 274.30 \times 100}{W \times LOD \times 10}$$~~

▲$$\frac{[(V_{NaOH} \times T_{NaOH}) - (V_{HCl} \times T_{HCl})] \times 0.5 \times 274.30 \times 100}{W \times (1 - LOD) \times 10}$$ ▲*USP30*

in which V_{NaOH} is the volume, in mL, of 0.5 N sodium hydroxide added; T_{NaOH} is the titer of the 0.5 N sodium hydroxide; V_{HCl} is the volume, in mL, of 0.5 N hydrochloric acid used; T_{HCl} is the titer of 0.5 N hydrochloric acid; W is the weight, in g, of Ensulizole taken; ▲100 is the percentage conversion factor;▲*USP30* and *LOD* is the percentage of loss on drying expressed as a weight fraction, as determined in the test for *Loss on drying.*■1S (*USP28*)

BRIEFING

Estradiol Vaginal Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Symmetry brand of L1 column. The typical retention time for estradiol is about 4.1 minutes.

(PA1: C. Anthony) RTS— 39955-1

Add the following:

▲Estradiol Vaginal Tablets

» Estradiol Vaginal Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol ($C_{18}H_{24}O_2$).

Packaging and storage—Each Tablet is contained in a single-unit HG-polyethylene/polyethylene applicator. Each applicator with the inset tablet is packed separately in a laminated blister consisting of aluminum and polyvinylchloride foil. Preserve in a tight container, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Estradiol RS. USP Estradiol Related Compound A RS. USP Estradiol Related Compound B RS. USP Estrone RS.*

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Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Place 30 Tablets in a vessel, add 500 mL of water, and allow to disintegrate by shaking overnight. Add 50.0 mL of ether, and shake for 2 minutes. Filter the ether layer through cotton wool and anhydrous sodium phosphate, shake with three 50-mL aliquots of ether, and evaporate to dryness. Dissolve the residue in 5 mL of ether, and quantitatively transfer to a fresh vessel. Evaporate to dryness, and reconstitute with 150 µL of absolute alcohol.

Standard solution—Dissolve suitable quantities of USP Estradiol RS, USP Estradiol Related Compound A RS, and USP Estrone RS, accurately weighed, in absolute alcohol to obtain a solution having known concentrations of 5 mg per mL, 0.25 mg per mL, and 0.25 mg per mL, respectively.

Application volume: 5 µL.

Developing solvent system: a mixture of chloroform and acetone (9 : 1).

Procedure—Proceed as directed in the chapter using the *Developing solvent system* described above. Develop the chromatogram three times over a path of about 8 cm, allowing the chromatogram to dry for 1 minute between each run. After the third run, allow the plate to air-dry. After removal of the plate, marking of the solvent front, and allowing solvent evaporation as described in the chapter, heat at 100° for about 15 minutes. Allow the plate to cool, and then immerse it in a mixture of absolute alcohol and concentrated sulfuric acid (95 : 5). Remove it immediately, place the plate on absorbing paper, and allow it to air-dry. Heat the plate at 100° until it is developed. Examine under UV light at $\lambda = 365$ nm. The principal spot obtained from the *Test solution* and the *Standard solution* has the same color and R_F value.

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.*

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g. Tablets meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Dissolution ⟨711⟩—[To come.]

Loss on drying ⟨731⟩—Dry about 1200 mg of finely powdered Tablets in a tared evaporating dish at a pressure not exceeding 25 mm of mercury at 60° for 3 hours: it loses not more than 7.0% of its weight.

Chromatographic purity—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (5 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Estradiol RS and USP Estradiol Related Compound B RS to obtain a solution having a known concentration of about 100 µg per mL and about 0.525 µg per mL, respectively.

Test solution—Place 12 Tablets, equivalent to about 300 µg of estradiol, in a 50-mL volumetric flask. Add 50 mL of absolute alcohol, stir for 16 hours with a magnetic stirrer, and shake thoroughly. Centrifuge the suspension, and evaporate 10.0 mL of the supernatant to dryness. Dissolve the residue in 1.0 mL of water and 7.0 mL of a mixture of toluene and acetone (5 : 2), mix on a whirl mixer, allow to stand for 1 hour, and evaporate 5 mL of the organic phase to dryness. The residue is reconstituted in 450 µL of absolute alcohol, to obtain a solution containing about 0.08 µg of estradiol per mL, and centrifuged.

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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 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.96 for estradiol related compound B and 1.0 for estradiol; and the resolution, *R,* between estradiol related compound B and estradiol is not less than 2.0.

Procedure—Inject a volume (about 25 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all the peak responses. Calculate the percentage of each estradiol related 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 3.0% of total impurities is found. The impurities meet the requirements specified in the table below.

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
6α-Hydroxy estradiol	0.54	1.0	1.0
6β-Hydroxy estradiol	0.60	1.0	1.0
6-Keto estradiol	0.71	1.0	1.0
16-Keto estradiol	0.74	1.0	1.0
6-Keto estrone	0.85	1.0	1.0
β-Equilenol	0.91	1.0	1.0
Estradiol related compound B (6-Dehydro-estradiol)	0.96	1.0	1.0
Estradiol	1.0	1.0	—
Estradiol related compound A (α-Estradiol)	1.05	1.0	1.0
Estrone	1.13	1.0	1.0
4-Methyl estradiol	1.17	1.0	1.0
Total impurities	—	—	1.0

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (5 : 1).

Solvent solution—Prepare a mixture of water and absolute alcohol (1 : 1).

Estrone standard stock solution—Prepare a solution of USP Estrone RS in absolute alcohol having a known concentration of 0.4 mg per mL.

Estradiol standard stock solution—Prepare a solution of USP Estradiol RS in absolute alcohol having a known concentration of 0.5 mg per mL.

System suitability preparation—Transfer 400 µL of *Estradiol standard stock solution* and 200 µL of *Estrone standard stock solution* to a 100-mL volumetric flask, and dilute to the mark with *Solvent solution*.

Standard solution—Pipet 500 µL of *Estradiol standard stock solution* into a 250-mL flask, and dilute with *Solvent solution* to the mark to obtain a solution having a known concentration of about 1.0 µg per mL.

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Assay preparation—Add 10 Tablets into a measured amount of *Solvent solution*, to obtain a solution having an estradiol concentration of about 2.5 µg per mL. Stir the mixture overnight with a magnetic stirrer, shake thoroughly, and centrifuge if necessary.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between estradiol and estrone 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 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatographs, and measure the peak responses. Calculate the quantity, in mg, of estradiol ($C_{18}H_{24}O_2$) in the portion of Tablets taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Estradiol RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and *Standard preparation,* respectively.▲*USP30*

BRIEFING

Synthetic Conjugated Estrogens. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed.

(PA1: C. Anthony) RTS—42243-1

Add the following:

▲Synthetic Conjugated Estrogens

» Synthetic Conjugated Estrogens is a mixture of sodium estrone sulfate and sodium equilin sulfate, derived synthetically from Estrone and Equilin. It contains other conjugated estrogenic substances of the type excreted by pregnant mares. It is a dispersion of the estrogenic substances in a suitable diluent.

Synthetic Conjugated Estrogens contains not less than 52.5 percent and not more than 61.5 percent of sodium estrone sulfate; not less than 22.5 percent and not more than 30.5 percent of sodium equilin sulfate; and not less than 13.5 percent and not more than 19.5 percent of sodium 17α-dihydroequilin sulfate. The total of sodium estrone sulfate, sodium equilin sulfate, and sodium17α-dihydroequilin sulfate is not less than 90.0 percent

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and not more than 110.0 percent of the labeled content of Synthetic Conjugated Estrogens. Synthetic Conjugated Estrogens contains not less than 2.5 percent and not more than 9.5 percent of sodium 17α-estradiol sulfate; and not less than 0.5 percent and not more than 4.0 percent of sodium 17β-dihydroequilin sulfate, of the labeled content of Synthetic Conjugated Estrogens. Synthetic Conjugated Estrogens A meets the requirements of Synthetic Conjugated Estrogens and contains not less than 0.1 percent and not more than 3.0 percent of sodium 17α-dihydroequilenin sulfate; not less than 0.1 percent and not more than 1.5 percent of sodium 17 β-dihydroequilenin sulfate; not less than 0.1 percent and not more than 4.0 percent of sodium equilenin sulfate; and not less than 0.1 percent and not more than 2.5 percent of sodium 17β-estradiol sulfate. Synthetic Conjugated Estrogens B meets the requirements of Synthetic Conjugated Estrogens A and contains not less than 1.0 percent and not more than 7.0 percent of sodium $\Delta^{8,9}$-dehydroestrone sulfate.

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label it to state the content of Synthetic Conjugated Estrogens on a weight-to-weight basis.

USP Reference standards ⟨11⟩**—***USP 17α-Dihydroequilin RS. USP Equilin RS. USP Estradiol RS. USP Estrone RS.*

Identification—The following results are obtained with respect to the *Assay preparation,* treated as directed for *Procedure* in the *Assay.*

A: The relative retention times of the major peaks for 17α-dihydroequilin, estrone, and equilin in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

B: The chromatogram of the *Assay preparation* exhibits additional peaks or shoulders, corresponding to 17α-estradiol and 17β-dihydroequilin at retention times of about 0.24 and 0.35, respectively, relative to that of 3-*O*-methylestrone.

Limit of estrone, equilin, and 17α-dihydroequilin (free steroids)—

Internal standard solution, pH 5.2 Acetate buffer, and *System suitability solution*—Proceed as directed in the *Assay.*

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

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

Free steroids standard solution—Dilute the *Standard stock solution* tenfold. Pipet 1.0 mL of the resulting solution and 1.0 mL of the *Internal standard solution* into a suitable centrifuge tube fitted with a tight screw cap or stopper. Proceed as directed for *Standard preparation* in the *Assay,* beginning with "Evaporate the mixture."

Test solution—Proceed as directed for *Assay preparation* in the *Assay* with the following exceptions: do not add the sulfatase enzyme preparation, and transfer 6.0 mL of the filtrate instead of 3.0 mL in the preparation of the test specimen.

Blank solution—Prepare as directed for the *Test solution,* without addition of the Synthetic Conjugated Estrogens.

Chromatographic system—Proceed as directed in the *Assay* with the additional requirement that for not less than two replicate injections the relative standard deviation for the ra-

tio of the peak response of estrone to that of the internal standard in the *Free steroids standard solution* is not greater than 5.5%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Free steroids standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the ratio, R_U, of the combined peak areas of estrone, equilin, and 17α-dihydroequilin relative to the area of the internal standard in the *Test solution,* correcting for peaks obtained from the *Blank solution.* The ratio, R_U / R_S, where R_S is the peak response ratio of estrone to that of the internal standard obtained from the *Free steroids standard solution,* is not more than 0.65 (1.3% of free steroids).

Limit of chromatographic impurities—

Internal standard solution, pH 5.2 Acetate buffer, System suitability solution, and *Chromatographic system*—Prepare as directed in the *Assay.*

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

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

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

Blank solution—Prepare as directed for the *Assay preparation* without addition of the Synthetic Conjugated Estrogens.

Procedure—Separately inject equal volumes (about 1 µL) of the *Test solution* and the *Blank solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Identify any peaks obtained from the *Blank solution* that are not due to the identified estrogenic components and are not due to the reagents in the *Blank solution.* For each peak response calculate the area percent using the formula:

$$100(A_R / A_T)$$

in which A_R is the sum of the unidentified area responses obtained from the *Blank solution,* and A_T is the sum of the area responses of the identified estrogenic components obtained from the *Test solution.* Calculate the area percentage of the chromatographic impurities by summing the area percentage determined for each response identified. The total area percentage of the responses is less than or equal to 1%.

Residual solvents ⟨467⟩**:** meets the requirements.

Solvent—Use dimethyl sulfoxide.

Content of 17α-dihydroequilin, 17β-dihydroequilin, and 17α-estradiol—

Internal standard solution, pH 5.2 Acetate buffer, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

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

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the peaks due to 17α-estradiol, 17α-dihydroequilin, and 17β-dihydroequilin in the chromatogram of the *Test solution.* The relative retention times of 17α-estradiol, 17α-dihydroequilin, and 17β-dihydroequilin are about 0.82, 1.00, and 1.11, respectively. Separately calculate the quantities, in mg, of

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17α-estradiol, 17α-dihydroequilin, and 17β-dihydroequilin as their sodium sulfate salts in the portion of Synthetic Conjugated Estrogens taken by the formula:

$$0.005(1.381C_S)(R_U/R_S)$$

in which C_S is the concentration, in µg per mL, of USP 17α-Dihydroequilin RS in the *Standard stock solution;* R_U is the ratio of the peak response of the appropriate analyte to that of the internal standard obtained from the *Test solution;* and R_S is the ratio of the peak response of 17α-dihydroequilin to that of the internal standard obtained from the *Standard solution.*

Content of 17α-dihydroequilenin, 17β-dihydroequilenin, and equilenin—

Internal standard solution, Stock solution, pH 5.2 Acetate buffer, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

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

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify any peaks due to17α-dihydroequilenin, 17β-dihydroequilenin, 3-*O*-methylestrone, and equilenin in the chromatogram of the *Test solution.* The relative retention times for 17α-dihydroequilenin, 17β-dihydroequilenin, 3-*O*-methylestrone, and equilenin are about 0.56, 0.64, 1.0, and 1.3 respectively. Separately calculate the quantities, in mg, of 17α-dihydroequilenin, 17β-dihydroequilenin, and equilenin as their sodium sulfate salts in the portion of Synthetic Conjugated Estrogens taken by the formula:

$$0.005(1.381C_S)(R_U/R_S)$$

in which C_S is the concentration, in µg per mL, of USP Estrone RS in the *Standard stock solution;* R_U is the ratio of the peak response of the appropriate analyte to that of the internal standard obtained from the *Test solution;* and R_S is the ratio of the peak response of estrone to that of the internal standard obtained from the *Standard solution.*

Content of 17β-estradiol and $\Delta^{8,9}$-dehydroestrone—

Internal standard solution, Stock solution, pH 5.2 Acetate buffer, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify any peaks due to 17β-estradiol, 3-*O*-methylestrone, and $\Delta^{8,9}$-dehydroestrone in the chromatogram of the *Test solution.* The relative retention times of 17β-estradiol, 3-*O*-methylestrone, and $\Delta^{8,9}$-dehydroestrone are about 0.29, 1.0, and 0.9, respectively. Separately calculate the quantities, in mg, of 17β-estradiol and $^{\Delta 8,9}$-dehydroestrone as their sodium sulfate salts in the portion of Synthetic Conjugated Estrogens taken by the formula:

$$0.005(1.381C_S)(R_U/R_S)$$

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in which C_S is the concentration, in µg per mL, of USP Estrone RS in the *Standard stock solution;* R_U is the ratio of the peak response of the appropriate analyte to that of the internal standard obtained from the *Test solution;* and R_S is the ratio of the peak response of estrone to that of the internal standard obtained from the *Standard solution.*

Assay—

Internal standard solution—Prepare a solution of 3-*O*-methylestrone in methanol containing about 150 µg per mL.

Standard stock preparation—Using accurately weighed quantities of USP Estrone RS, USP Equilin RS, and USP 17α-Dihydroequilin RS, prepare, by quantitative and stepwise dilution, a solution in alcohol having known concentrations of about 160 µg per mL, 70 µg per mL, and 50 µg per mL, respectively.

pH 5.2 Acetate buffer—Mix 79 mL of sodium acetate TS with 21 mL of 1 N acetic acid, dilute with water to 500 mL, and mix. Adjust to a pH of 5.2 ± 0.1 by the addition of 1 N acetic acid or sodium acetate TS, if necessary.

System suitability solution—Dissolve a quantity of USP Estradiol RS (17β-estradiol) in alcohol to obtain a solution containing about 2 µg per mL. Pipet 1.0 mL of this solution, 1.0 mL of *Standard stock preparation,* and 1.0 mL of *Internal standard solution* into a centrifuge tube fitted with a tight screw cap or stopper. Proceed as directed for *Standard preparation,* beginning with "Evaporate the mixture."

Standard preparation—Pipet 1.0 mL of the *Standard stock preparation* and 1.0 mL of the *Internal standard solution* into a suitable centrifuge tube fitted with a tight screw cap or stopper. Evaporate the mixture with the aid of a stream of nitrogen to dryness, maintaining the temperature below 50°. To the dry residue add 15 µL of dried pyridine and 65 µL of bis(trimethylsilyl)trifluoroacetamide containing 1% trimethylchlorosilane. Immediately cover the tube tightly, mix, and allow to stand for 15 minutes. Add 0.5 mL of toluene, and mix.

Assay preparation—Transfer an accurately weighed quantity of Synthetic Conjugated Estrogens, equivalent to about 2 mg of total synthetic conjugated estrogens, to a 100-mL square bottle, fitted with a polytef-lined screw cap, containing 15 mL of *pH 5.2 Acetate buffer* and 1 g of barium chloride (1 : 3 aqueous solution). Cap the tube tightly, and shake by mechanical means for 30 minutes. If necessary, adjust the solution with 1 N acetic acid or sodium acetate to a pH of 5.0 ± 0.5. Place in a sonic bath for 30 seconds, then shake for an additional 30 minutes. Add a suitable sulfatase enzyme preparation equivalent to 2500 Units, and shake for 20 minutes in a water bath maintained at 50°. Add 15.0 mL of ethylene dichloride to the warm mixture, cap the tube again, and shake for 15 minutes. Centrifuge for 10 minutes or until the lower layer is clear. Transfer as much of the organic phase as possible, and dry by passing rapidly through a filter consisting of a pledget of dry glass wool and about 5 g of anhydrous sodium sulfate in a small funnel. Protect from loss due to evaporation. Transfer 3.0 mL of the solution to a suitable centrifuge tube fitted with a tight screw cap or stopper. Add 1.0 mL of *Internal standard solution.* Proceed as directed for *Standard preparation,* beginning with "Evaporate the mixture."

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector maintained at a temperature of 260°, a 0.25-mm × 15-m fused silica capillary column bonded with a 0.25-µm layer of phase G19, and a split injection system. The column temperature is maintained at 220° and the injection port is maintained at 260°. The carrier gas is hydrogen flowing at the rate of 2 mL per minute, and the split flow rate is 40 to 60 mL per minute. Inject about 1 µL of the *System suitability*

solution into the gas chromatograph, adjust the operating conditions as necessary to maintain the elution time of the 3-*O*-methylestrone peak at between 17 and 25 minutes, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.29, 0.30, 0.80, 0.87, and 1.00 for 17β-estradiol, 17α-dihydroequilin, estrone, equilin, and 3-*O*-methylestrone, respectively; the resolution, *R,* between estrone and equilin is not less than 1.2; and the tailing factor for the estrone peak is not more than 1.3. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation of the estrone peak ratios for not fewer than four injections is not greater than 2.0%.

Procedure—Separately inject equal volumes (about 1 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 quantities, in mg, of sodium estrone sulfate and sodium equilin sulfate in the portion of Synthetic Conjugated Estrogens taken by the formula:

$$0.005(1.381C_S)(R_U/R_S)$$

in which 1.381 is the factor converting free estrogen to the conjugate sodium salt; C_S is the concentration, in µg per mL, of USP Estrone RS or USP Equilin RS in the *Standard stock preparation;* and R_U and R_S are the ratios of the peak response of the appropriate analyte to that of the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Etidronate Disodium, *USP 28* page 798, and page 3485 of the *Second Supplement*. It is proposed to allow the use of a suitable chemical suppressor in the test for *Limit of phosphite,* in addition to a self-regenerating suppressor. A *Note* has been added to clarify that the *Suppressor regenerant solution* is needed only when the chemical suppression option is used.

(MD-GRE: E. Gonikberg) RTS—43210-1

Change to read:

Limit of phosphite—

■*Solution A*—Prepare an aqueous solution containing 0.65 mg per mL of anhydrous sodium carbonate and 0.40 mg per mL of sodium bicarbonate.

Solution B—Prepare an aqueous solution containing 4.68 mg per mL of anhydrous sodium carbonate and 2.89 mg per mL of sodium bicarbonate.

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 suitable quantities of USP Etidronate Disodium Related Compound A RS and dibasic sodium phosphate in *Solution A* to obtain a solution having a known concentration of 0.027 mg of sodium phosphite dibasic pentahydrate and 0.015 mg of dibasic sodium phosphate in each mL. [NOTE—Etidronate disodium related compound A is sodium phosphite dibasic pentahydrate.]

Suppressor regenerant solution—Use 12.5 mM sulfuric acid.

▲[NOTE—This solution is needed only if the chemical suppression option is used.]▲*USP30*

Test solution—Transfer approximately 50 mg of Etidronate Disodium, accurately weighed, to a suitable flask. Dissolve in 10.0 mL of *Solution A*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector, a 4-mm × 25-cm column and a 4-mm × 50-mm guard column ~~that contain packing L61, and a 4-mm anion self-regenerating suppressor~~ ▲both containing packing L61, and either a 4-mm anion self-regenerating suppressor or a suitable chemical suppressor.▲*USP30*

The flow rate is about 1.0 mL per minute for the *Mobile phase*. ~~and 3 to 5 mL per minute for the *Suppressor regenerant solution.*~~ ▲When a chemical suppressor is used, the flow rate is 3 to 5 mL per minute for the *Suppressor regenerant solution.*▲*USP30*

The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6.0	100	0	isocratic
6.0–6.1	100→0	0→100	linear gradient
6.1–8.0	0	100	isocratic
8.0–8.1	0→100	100→0	linear gradient
8.1–15	100	0	isocratic

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Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the elution order is phosphite, followed by phosphate; the resolution, *R,* between phosphite and phosphate is not less than 2.5; and the relative standard deviation for replicate injections is not more than 10% for each peak.

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 phosphite peaks. Calculate the percentage of phosphite, determined as monobasic sodium phosphite, in the portion of Etidronate Disodium taken by the formula:

$$1000(103.98/216.06)(C/W)(r_U/r_S)$$

in which 103.98 and 216.06 are the molecular weights of sodium phosphite monobasic and sodium phosphite dibasic pentahydrate, respectively; C is the concentration, in mg per mL, of USP Etidronate Disodium Related Compound A RS in the *Standard solution;* W is the weight, in mg, of Etidronate Disodium taken to prepare the *Test solution;* and r_U and r_S are the phosphite peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.0% of phosphite, determined as monobasic sodium phosphite, is found. ■2S (*USP28*)

BRIEFING

Fentanyl. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a Microsorb C18 brand of L1 column. The typical retention time for fentanyl is about 2.7 minutes.

(PA2: C. Anthony) RTS—42140-1

Add the following:

▲Fentanyl

$C_{22}H_{28}N_2O$ 336.47

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl].

N-(1-Phenethyl-4-piperidyl)propionanilide. [*437-38-7*].

» Fentanyl contains not less than 98.0 percent and not more than 102.0 percent of the labeled amount of $C_{22}H_{28}N_2O$, calculated on the dried basis.

Caution—Great care should be taken to prevent inhaling particles of Fentanyl and exposing the skin to it.

Packaging and storage—Preserve in tightly closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—***USP Fentanyl RS. USP Fentanyl Related Compound A RS. USP Fentanyl Related Compound B RS. USP Fentanyl Related Compound C RS. USP Fentanyl Related Compound D RS. USP Fentanyl Related Compound E RS. USP Fentanyl Related Compound F RS. USP Fentanyl Related Compound G 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.*

Loss on drying ⟨731⟩**—**Dry it in vacuum at 60° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.5%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Standard stock solution—Dissolve an accurately weighed quantity of USP Fentanyl Related Compound A RS, USP Fentanyl Related Compound B RS, USP Fentanyl Related Compound C RS, USP Fentanyl Related Compound D RS, USP Fentanyl Related Compound E RS, USP Fentanyl Related Compound F RS, and USP Fentanyl Related Compound G RS in methanol to obtain a solution having a known concentration of each related compound of about 0.13 mg per mL.

Standard solution—Prepare a 1 : 5 dilution of *Standard stock solution* in methanol.

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Test solution—Transfer 250 mg of Fentanyl, accurately weighed, to a 10-mL volumetric flask, and dissolve in methanol.

Spiked test solution—Transfer 250 mg of Fentanyl, accurately weighed, to a 10-mL volumetric flask, and dissolve in *Standard stock solution.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame ionization detector and a 0.32-mm × 30-m column containing a 0.5-µm layer of phase G3. The carrier gas is helium, flowing at a rate of about 2.4 mL per minute, and the split ratio is about 30 : 1. The chromatograph is programmed as follows. Initially the temperature of the column is equilibrated at about 220° for 2.5 minutes, then the temperature is increased at a rate of 8° per minute to 275°, and maintained at 275° for 26 minutes. The equilibration time is 2 minutes. The injector and detector port temperatures are maintained at 280°. Chromatograph the *Spiked test solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six replicate injections is not more than 5% for each impurity.

Procedure—Separately inject equal volumes (about 3 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the peak responses. Impurity peak responses are normalized to adjust for different drug weights. Determine the concentration, in µg per mL, of each impurity obtained from the chromatogram of the *Test solution* . Then calculate the content of each related compound in % (w/w) by using the following equations:

$$(n)A_S = A_S \times C_T / C_S$$

$$X_i = A_T \times C_i / [(n)A_S - A_T]$$

$$\% (w/w) = X_i \times 100 / C_T$$

in which $(n)A_S$ is the normalized peak area of the related compound obtained from the chromatogram of the *Spiked test solution,* A_S is the peak area of of the related compound obtained from the *Spiked test solution,* and A_T is the peak area of the related compound obtained from the *Test solution;* C_T and C_S are the concentrations of fentanyl, in µg per mL, in the *Test solution* and the *Spiked test solution,* respectively; C_i is the concentration, in µg per mL, of the related compound in the *Standard stock solution*; X_i is the calculated concentration, in µg per mL, of each related compound in the *Test solution.*

Calculate impurity content in % (w/w) by using the following equations:

$$(n)A_{ki} = A_{ki} \times C_T / C_S$$

$$EC_{uk} = A_{uk} \times C_{ki} / [(n)A_{ki} - A_{ki}]$$

$$\text{Unknown Impurity } \% = EC_{uk} \times 100 / C_T$$

in which $(n)A_{ki}$ is the normalized peak area of a known impurity obtained from the chromatogram of the *Spiked test solution,* A_{ki} is half the peak area of the nearest known impurity in the chromatogram of the *Spiked test solution,* and A_{uk} is the peak area of an unknown impurity obtained from the chromatogram of the *Test solution;* C_T and C_S are the concentrations, in µg per mL, of fentanyl in the *Test solution* and the *Spiked test solution,* respectively; EC_{uk} is the estimated concentration of an unknown impurity in the *Test solution;* and C_{ki} is the concentration, in µg per mL, of a known impurity in the *Test solution:* the impurities meet the requirements specified in the table below.

Name	Relative Retention Times	Limits (%)
USP Fentanyl Related Compound A	0.17	0.25
USP Fentanyl Related Compound B	0.44	0.25
USP Fentanyl Related Compound C	0.59	0.25
USP Fentanyl Related Compound D	0.72	0.25
USP Fentanyl Related Compound E	0.78	0.25
USP Fentanyl Related Compound F	0.89	0.25
USP Fentanyl Related Compound G	0.96	0.25
Individual unknown impurities	NA	0.1
Total impurities	NA	0.5

Residual solvents ⟨467⟩**:** meets the requirements.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, triethylamine, phosphoric acid, and octanesulfonic acid (500 : 500 : 1 : 1 : 0.5)

Diluent—Prepare a 0.02 N sulfuric acid solution.

Standard preparation—Dissolve an accurately weighed quantity of USP Fentanyl RS in *Diluent* to obtain a solution having a known concentration of about 15 µg per mL.

System suitability solution—Dissolve accurately weighed quantities of Fentanyl and USP Fentanyl Related Compound G RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a concentration of 10 µg per mL of fentanyl base and 1 µg per mL of USP Fentanyl Related Compound G RS.

Assay preparation—Dissolve an accurately weighed quantity of Fentanyl in *Diluent* to obtain a solution having a known concentration of about 15 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-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 tailing factor for the fentanyl peak is not greater than 2.0. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fentanyl and fentanyl related compound G is not less than 1.5; and the relative standard deviation for replicate injections is not greater than 2.0% for fentanyl.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in percent, of $C_{22}H_{28}N_2O$ in the portion of Fentanyl taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL of USP Fentanyl RS in the *Standard preparation;* C_U is the concentration of Fentanyl in the *Assay preparation;* and r_U and r_S are the peak responses of fentanyl in the *Assay preparation* and *Standard preparation,* respectively.▲*USP30*

BRIEFING

Flumazenil, page 3230 of the *First Supplement.* It is proposed to replace Chlordiazepoxide, a Class IV controlled substance, with USP Flumazenil Related Compound B, for use in preparation of the *System suitability solution* in the *Assay.* In addition, it is proposed to revise the preparation of the *Standard solution* in *Related compounds Test 2* by using a diluted solution of the *Standard preparation* from the *Assay* instead of weighing out an additional quantity of USP Flumazenil RS. In *Related compounds Test 2,* it is further proposed to simplify preparation of the *Test solution* by using the *Assay preparation* and also to clarify the definition of the relative response factors specified in the *Procedure.* Finally, in *Re-*

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lated compounds Test 2 and in the *Assay,* it is proposed to revise the formula to reflect the use of the drug substance concentration rather than its weight.

(MD-PP: R. Ravichandran) RTS—43186-1

Change to read:

USP Reference standards ⟨11⟩—*USP Flumazenil RS.*

▲*USP Flumazenil Related Compound B RS.*▲*USP30*

Change to read:

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—Prepare a solution of USP Flumazenil RS and *N,N*-dimethylformamide diethyl acetal in *Diluent* having known concentrations of about 0.5 mg per mL and about 0.6 µL per mL, respectively.

Standard solution 2—Dilute 2.0 mL of *Standard solution 1* 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).

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
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 2:* not more than 0.2% is found.

TEST 2—

Diluted phosphoric acid, pH 2.0, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—~~Dissolve an accurately weighed quantity of USP Flumazenil RS in *Mobile phase,* and dilute quantitatively,~~

▲Dilute the *Standard preparation* quantitatively,▲*USP30* and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL of flumazenil.

Test solution—~~Transfer about 25.0 mg of Flumazenil, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

▲Use the *Assay preparation.*▲*USP30*

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least three times the retention time of the flumazenil peak, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Flumazenil taken by the formula:

~~$2500(C/W)(1/F)(r_i/r_s),$~~

▲$100(C_S/C_U)(r_i/r_S)(1/F)$▲*USP30*

~~in which *C* is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard solution; F* is the relative response factor according to the *Table* below; *W* is the weight, in mg, of Flumazenil, 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 flumazenil in the *Standard solution;* the impurities meet the requirements given in the *Table* below.~~

▲in which C_S and C_U are the concentrations, in mg per mL, of flumazenil in the *Standard solution* and the *Test solution,* respectively; r_i is the peak area for any impurity in the *Test solution;* r_S is the peak area for flumazenil in the *Standard solution;* and F is the relative response factor for each of the known impurities relative to flumazenil. [NOTE—F values are given for all the impurities, along with the corresponding limits, in the *Table* below.]▲*USP30*

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Flumazenil related compound A	about 0.4	1.1	0.2
7-Fluoro-4-methyl-3,4-dihydro-2,5*H*-1,4-benzodiazepine-2,5-dione	about 0.5	1.5	0.2
Ethyl 5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxylate	about 0.7	1.3	0.2
Flumazenil related compound B	about 0.8	1.1	0.2
Flumazenil	1.0	—	—
Ethyl 8-chloro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxylate	about 2.2	1.1	0.2
Any individual unknown impurity	—	1.0	0.1
Total	—	—	0.5

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Change to read:

Assay—

Diluted phosphoric acid, pH 2.0—Adjust 800 mL of water with phosphoric acid to a pH of 2.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Diluted phosphoric acid, pH 2.0,* methanol, and tetrahydrofuran (80 : 13 : 7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve appropriate quantities of ~~chlordiazepoxide and~~

▲*USP30*
USP Flumazenil RS

▲and USP Flumazenil Related Compound B▲*USP30*
in *Mobile phase,* and dilute, stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 6.4 µg per mL of each compound.

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 1.0 mg per mL

▲of flumazenil.▲*USP30*

Assay preparation—Transfer about 25.0 mg of Flumazenil, accurately weighed, to a 25-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 × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph

▲5 µL of▲*USP30*
the *System suitability solution,* and record the peak responses: ~~as directed for *Procedure:*~~

▲▲*USP30*
the relative retention times are about ~~0.82 for chlordiazepoxide~~

▲0.8 for flumazenil related compound B▲*USP30*
and 1.0 for flumazenil; the resolution, *R,* between ~~chlordiazepoxide~~

▲flumazenil related compound B▲*USP30*
and flumazenil is not less than ~~2.0~~

▲4.0;▲*USP30*
the column efficiency is not less than 1500 theoretical plates for the flumazenil peak; and the tailing factor is not more than 1.5 for the flumazenil peak. Chromatograph

▲5 µL of▲*USP30*
the *Standard preparation,* and record the peak responses: ~~as directed for *Procedure:*~~

▲▲*USP30*
the relative standard deviation for replicate injections is not more than 2.0%.

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 flumazenil peaks. ~~Calculate the quantity, in mg, of $C_{13}H_{11}FN_2O_2$ in the portion of Flumazenil taken by the formula:~~

~~$25C(r_U/r_S),$~~

▲Calculate the percentage of $C_{15}H_{14}FN_3O_3$ in the portion of Flumazenil taken by the formula:

$$100(C_S/C_U)(r_U/r_S)_{▲USP30}$$

in which ~~*C* is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard preparation;*~~

▲C_S and C_U are the concentrations, in mg per mL, of flumazenil in the *Standard preparation* and the *Assay preparation,* respectively;▲*USP30*
and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Gemcitabine for Injection, *USP 28* page 893 and page 3238 of the *First Supplement*. It is proposed to revise the test for *Chromatographic purity* to indicate that r_S is the peak response for gemcitabine in the *Standard solution*. Also, editorial changes are being proposed to specify that r_i is the peak response for the gemcitabine α-anomer or any other individual impurity in the *Test solution* and that the USP Cytosine RS, which is specified in this test, is added to the *Reference standards* section.

(MD-OOD: L. Evans) RTS—43292-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Cytosine RS.*▲*USP30*
USP Endotoxin RS. USP Gemcitabine Hydrochloride RS.

Change to read:

Chromatographic purity—

Mobile phase, System suitability solution, Standard solution, and *Chromatographic system*—Proceed as directed in 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.

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Procedure—Proceed as directed in *Chromatographic purity* for *Gemcitabine Hydrochloride*. Calculate the amount of cytosine, expressed as a percentage of gemcitabine hydrochloride, by the formula:

$$0.1(263.20/299.66)(C_C V/L)(r_t / r_S)$$

in which 263.20 and 299.66 are the molecular weights of gemcitabine and gemcitabine hydrochloride, respectively; C_C is the concentration of USP Cytosine RS in the *Standard solution,* in µg per mL; 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; 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:

$$0.1(263.20/299.66)(C_S V/L)(r_i / r_S)$$

in which 263.20 and 299.66 are the molecular weights of gemcitabine and gemcitabine hydrochloride, respectively; C_S is the concentration of USP Gemcitabine Hydrochloride RS in the *Standard solution,* in µg per mL; 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; r_i is the response for gemcitabine α-anomer or any other individual impurity

▲in the *Test solution;* ▲*USP30*
and r_S is the peak response for gemcitabine in the ~~*Test solution.*~~

▲*Standard solution.* ▲*USP30*
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%).

BRIEFING

Glipizide and Metformin Hydrochloride Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the tests for *Assay for glipizide* and *Related compounds (Glipizide)* is based on analyses performed with the Phenomenex Luna C8 brand of L7 column. The typical retention time for glipizide peak is about 14 minutes. The liquid chromatographic procedure in the tests for *Assay for metformin hydrochloride* and *Chromatographic purity (Metformin Hydrochloride)* is based on analyses performed with the Zorbax SB-Phenyl brand of L11 column. The typical retention time for metformin peak is about 7.5 minutes.

(PA4: E. Gonikberg; NL: W. Paul) RTS—42796-1

Add the following:

▲Glipizide and Metformin Hydrochloride Tablets

» Glipizide and Metformin Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of glipizide ($C_{21}H_{27}N_5O_4S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Glipizide RS. USP Glipizide Related Compound A RS. USP Metformin Hydrochloride RS. USP Metformin Related Compound A RS.*

Identification—

A: GLIPIZIDE—

Infrared Absorption ⟨197A⟩—Prepare the test specimen as follows. Transfer not fewer than 10 Tablets to a suitable container, add 10 mL of methanol, and shake to remove any tablet coating. Drain the methanol, add 20 mL of water, and stir until the Tablets dissolve (about 1 hour). Transfer the solution to a separatory funnel, and extract twice with 10-mL portions of chloroform, shaking for approximately 5 minutes. Transfer the lower organic layer into a beaker containing 3 to 4 g of anhydrous magnesium sulfate. Repeat the extraction of the solution in the separatory funnel two more times, each time using 20-mL portions of chloroform. Swirl the mixture in the beaker for about 1 minute. Filter, and collect the filtrate. Evaporate the solvent under vacuum, and dry the residue under vacuum for 4 hours at 105°. Mound

the residue onto a diamond cell: the IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Glipizide RS.

B: GLIPIZIDE—

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 for glipizide.*

C: METFORMIN HYDROCHLORIDE—

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 for metformin hydrochloride.*

Dissolution ⟨711⟩—[To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

GLIPIZIDE—

Solution A, Solution B, and *Chromatographic system*—Prepare as directed in the *Assay for glipizide*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for glipizide*.

Procedure—Inject about 50 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of glipizide related compound A (approximate relative retention time 0.92) and other individual impurities in the portion of Tablets taken by the formula:

$$100(1/F)(r_i / r_s)$$

in which F is the relative response factor for each impurity and is equal to 1.4 for glipizide related compound A and 1.0 for all other peaks; r_i is the peak response of each impurity; and r_s is the sum of the responses of all the peaks: not more than 2.0% of glipizide related compound A is found; not more than 0.5% of any other individual glipizide related impurity (eluting after approximately 8 minutes) is found; and not more than 1.0% total impurities, excluding glipizide related compound A, is found. [NOTE—Disregard the broad peak due to metformin that elutes before 8 minutes. Disregard any peak observed in the blank, and disregard any peak less than 0.05%.]

Chromatographic purity—

METFORMIN HYDROCHLORIDE—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay for metformin hydrochloride*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for metformin hydrochloride.*

Procedure—Inject about 25 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 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Assay for glipizide—

Ammonium phosphate buffer pH 8.0—Dissolve 2.6 g of dibasic ammonium phosphate in water, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 8.0.

Solution A—Prepare a degassed mixture of water, *Ammonium phosphate buffer pH 8.0,* and acetonitrile (14 : 5 : 1).

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Solution B—Prepare a degassed mixture of acetonitrile, *Ammonium phosphate buffer pH 8.0,* and water (2 : 1 : 1).

Diluent—Use a mixture of acetonitrile and water (60 : 40).

Standard stock preparation—Transfer an accurately weighed quantity of USP Glipizide RS to a suitable low-actinic volumetric flask. Dissolve first in acetonitrile, using 60% of the final volume, by sonicating for about 20 minutes, then dilute with water to volume to obtain a solution having a known concentration of about 0.1 mg of glipizide per mL. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

Standard preparation—Transfer 25.0 mL of *Standard stock preparation* to a 200-mL low-actinic volumetric flask. Dilute first with 75 mL of *Diluent,* and bring to volume with water to obtain a solution having a known glipizide concentration of approximately 0.0125 mg per mL. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

System suitability preparation—Transfer approximately 5 mg of USP Glipizide Related Compound A RS to a 500-mL volumetric flask, and fill halfway with acetonitrile. Sonicate for about 30 minutes to dissolve, and dilute with acetonitrile to volume. Transfer 1 mL of this solution to a 50-mL low-actinic volumetric flask, and dilute with *Standard preparation* to volume.

Assay preparation—Transfer not fewer than 5 Tablets to a suitable volumetric flask, and fill halfway with *Diluent*. Sonicate for 30 minutes, and shake vigorously for another 30 minutes to dissolve. Dilute with water to volume, and mix to obtain a solution with a final glipizide concentration of about 0.0125 mg per mL. Pass a portion of this solution through a nylon or PVDF filter having a 0.2-µm porosity, and use the filtrate. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 223-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. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3	100	0	isocratic
3–18	100→0	0→100	linear gradient
18–20	0	100	isocratic
20–22	0→100	100→0	linear gradient
22–30	100	0	re-equilibration

Chromatograph the *System suitability preparation* and the *Standard preparation,* and record the peak responses as directed for *Procedure*. For the *System suitability preparation,* the relative retention times are about 0.92 for glipizide related compound A and 1.0 for glipizide; the resolution, *R,* between glipizide related compound A and glipizide is greater than 1.2. For the *Standard preparation,* the relative standard deviation for replicate injections is less 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 glipizide peaks. Calculate the quantity, in mg per Tablet, of glipizide ($C_{21}H_{27}N_5O_4S$) by the formula:

$$CV(r_U / r_S) / N$$

in which C is the concentration, in mg per mL, of USP Glipizide RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* r_U and r_S are the glipizide

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peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets taken to prepare the *Assay preparation.*

Assay for metformin hydrochloride—

Solution A—Prepare a 50 mM hexanesulfonic acid solution by dissolving 9.41 g of sodium 1-hexanesulfonate in 1000 mL of water, and adjusting with trifluoroacetic acid to a pH of 2.0.

Solution B—Prepare a solution of water and acetonitrile (60 : 40).

Mobile phase—Prepare a degassed mixture of water, *Solution A,* and *Solution B* (50 : 30 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent pH 2.0—Prepare a mixture of water, *Solution A*, and acetonitrile (63 : 30 : 7).

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent pH 2.0* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability preparation—Dissolve a suitable quantity of USP Metformin Related Compound A RS in water to obtain a solution containing about 5 µg per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay preparation—Quantitatively dilute a portion of the *Assay preparation,* obtained as directed for *Assay for glipizide,* with *Diluent pH 2.0,* to obtain a solution having an expected concentration of about 0.1 mg of metformin hydrochloride per mL, based on the label claim. Pass a portion of this solution through a nylon or PVDF filter having a 0.2-µm porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.26 for metformin related compound A and 1.0 for metformin; the resolution, *R,* between the two peaks is not less than 3.0; and the relative standard deviation for replicate injections, determined from the metformin peak, is less 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 per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$CVD(r_U / r_S)/N$$

in which *C* is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation*, as prepared under the *Assay for glipizide; D* is the dilution factor of the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets used to prepare the *Assay preparation.* ▲*USP30*

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BRIEFING

Glucagon, *USP 28* page 905 and page 3491 of the *Second Supplement.* Several changes in the *Assay* are proposed. Because of variability in this bioassay, it is proposed to allow for changes in concentrations of the *Standard preparations* and the *Assay preparations* to allow the *Assay* to be performed in a more linear portion of the response when needed. It is also proposed, on the basis of data and analysis received, to allow full curve analysis using validated nonlinear statistical methods. Finally, on the basis of analysis of data received from several laboratories, it is also proposed to change the criterion for the determination of linearity. It is proposed to implement these revisions via the *Second Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2006.

(BB PP: L. Callahan) RTS—43267-1; 43280-1

Change to read:

Assay—[NOTE—All buffers have a final pH of 7.4, unless otherwise indicated.

•The concentration range of the *Standard preparations* and the *Assay preparations* may be modified to fall within the linear range of the *Assay.* The calculations should be adjusted accordingly. Alternatively, full curve analysis using validated nonlinear statistical methods can be used, provided that parallelism is demonstrated when comparing the responses of the *Standard preparations* and the *Assay preparations*.]•2

HEPATOCYTE PREPARATION—

Calcium-free perfusion buffer with dextrose—Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 1.80 g of dextrose, 0.19 g of edetic acid, and 2.38 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid. Oxygenate prior to circulation.

Collagenase buffer—Prepare a solution containing, in each L, 3.62 g of sodium chloride, 23.83 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, 0.35 g of potassium chloride, 0.52 g of calcium chloride, and 1.8 g of dextrose. Adjust to a pH of 7.6, and oxygenate. Immediately before perfusion, dissolve a quantity of collagenase in this solution to obtain a concentration of 0.02% to 0.05%.

Wash buffer—Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 0.19 g of edetic acid, 2.38 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, 0.22 g of calcium chloride, and 0.12 g of magnesium sulfate.

Incubation buffer—Prepare a solution containing, in each L, 6.19 g of sodium chloride, 0.35 g of potassium chloride, 0.22 g of calcium chloride, 0.12 g of magnesium sulfate, 0.16 g of monobasic potassium phosphate, 11.915 g of *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid, and 1% bovine serum albumin (BSA). Adjust to a pH of 7.5.

Test animals—Male Sprague-Dawley rats are maintained on a standard rat chow diet and freely given water. On the morning of the test, select a healthy rat weighing approximately 300 g, and administer 100 Units of Heparin Sodium subcutaneously.

Procedure—[NOTE—Conduct this procedure in the morning to ensure that the rat has optimal glycogen in its liver.] Anesthetize the rat with an appropriate anesthetic. Open the abdominal cavity, and isolate the portal vein. Insert an angiocatheter connected to a perfusion pump, and tie into the portal vein at the general location of the lienal branch. Start the perfusion (25 mL per minute) in situ with *Calcium-free perfusion buffer with dextrose,* equilibrated with oxygen, at a temperature of 37°. As the liver enlarges, cut the inferior vena cava to allow pressure equilibrium. [NOTE—About 300 mL of the perfusate is needed to clear the liver of red blood cells at a flow rate of 30 to 60 mL per minute.] Then circulate *Collagenase buffer* at a flow rate of 30 to 60 mL per minute for about 10 minutes. The exact concentration of collagenase (within the range of 0.02% to 0.05%) is determined empirically for each lot of enzyme. The concentration of collagenase is that necessary to consistently cause a breakdown of the liver about 10 minutes after initial entry of the *Collagenase buffer* into the liver. When the liver significantly increases in size, changes color and consistency, and starts to leak perfusate out of the lobes, change the system to the oxygenated prewarmed *Wash buffer.* About 100 mL of *Wash buffer* is needed to wash the liver of collagenase at a flow rate of 25 mL per minute. Surgically remove the liver from the animal and place in a prewarmed tray containing oxygenated *Wash buffer* (37°). Gently comb the liver with a stainless steel, fine-toothed comb to free the hepatocytes. Wash the hepatocytes with *Wash buffer,* and filter through cheesecloth (or a 150-µm mesh polyethylene net) into a plastic beaker. Centrifuge the cell suspension for about 2 minutes at about 25 × *g* to form a loosely packed pellet. Discard the supernatant, and resuspend the pellet in *Wash buffer.* Repeat the washing procedure twice for a total of three washes. Resuspend the final pellet in 100 to 200 mL of *Incubation buffer,* depending on cell yield. [NOTE—If the *Assay* procedure is interrupted, cool the cells by collecting the cells in a beaker placed in ice. The cells are washed with ice-cold *Wash buffer,* and stored on ice until ready for use. At that point the cells are pelleted once more, and resuspended in ice-cold *Incubation buffer.*]

Suitability—The concentrations of cells may vary due to the collagenase activity and the viability of the hepatocytes. To check cell viability and to determine viable cell concentration, dilute duplicate 100-µL aliquots of cell suspension with 400 µL of *Wash buffer* and 500 µL of isotonic 0.4% trypan blue. The aliquots are counted in a hemocytometer. The cells are suspended in *Incubation buffer* to obtain a viable cell concentration of not less than 3×10^6 per mL. Count several distinct fields. [NOTE—Viable cells are those cells that exclude the trypan blue.]

NEGATIVE CONTROL SOLUTION—Prepare a solution containing 0.5% BSA in sterile water.

INCUBATION FLASKS—Use 25-mL conical flasks, the bottoms of which have been heated and pushed inward to form a conically raised center.

STANDARD PREPARATIONS—In duplicate, dissolve a suitable quantity of USP Glucagon RS, accurately measured, in 0.01 N hydrochloric acid or other suitable diluent to obtain a solution containing 1.0 USP Glucagon Unit per mL. All dilutions thereafter are made using 0.5% BSA (w/v) in water. Accurately dilute measured volumes of each solution with *Negative control solution* to obtain five concentrations—200, 100, 50, 25, and 12.5 micro-Units per

mL—of each solution *(Standard preparations).* Pipet 0.2 mL of each *Standard preparation* into separate *Incubation flasks.* Pipet 0.2 mL of *Negative control solution* into each of two flasks *(Negative control solutions 1* and *2).* Then add the hepatocytes into each of the 12 flasks.

ASSAY PREPARATIONS—Using accurately weighed quantities of Glucagon, proceed as directed for *Standard preparations.*

D-GLUCOSE DETERMINATION—

Standard stock solution—Transfer 2.0 g of USP Dextrose RS, accurately weighed, to a 200-mL volumetric flask, and dissolve in and dilute with saturated benzoic ■acid■2S *(USP28)* solution to volume.

Standard solutions—Transfer suitable quantities of *Standard stock solution* to three flasks, and dilute with saturated benzoic acid solution to obtain solutions having known concentrations of 0.5, 1.0, and 1.5 times the typical sample glucose concentration.

Potassium ferrocyanide solution—Dissolve 1.25 g of trihydrate potassium ferrocyanide in 125 mL of *Sterile Water for Injection*.

System suitability—Analyze the *Potassium ferrocyanide solution,* the *Standard solutions,* and five replicates of the middle *Standard solution.* Prepare a standard curve using the *Standard solutions* as directed for *Procedure:* the relative standard deviation of the standard curve is not more than 2.0%; the response of the *Potassium ferrocyanide solution* is not more than 30 mg per L; and the relative standard deviation is not more than 2.0% for the replicate analyses of the middle *Standard solution.*

PROCEDURE—Dispense 5 mL of *Hepatocyte preparation* into the special incubation flasks in sequence from high glucagon concentration to low glucagon concentration, alternating the *Standard preparations* with the *Assay preparations.* The flasks are swirled in an orbiting water bath at 125 rpm at 30° for approximately 30 to 60 minutes. [NOTE—The exact incubation time must be determined to optimize the signal-to-noise ratio.] Following incubation, place 0.5- to 1.0-mL aliquots, in duplicate, from each incubation flask into labeled tubes, and centrifuge at 12,500 × *g.* Determine the percentage of glucose concentration in each flask's supernatant.

To conform to the linear range of the instrument being used, it may be necessary to adjust by dilution each of the preparations. Use a glucose analyzer that has demonstrated appropriate specificity, accuracy, precision, and linear response over the range of concentrations being determined. [NOTE—A suitable analyzer may use an immobilized, oxidase-enzyme membrane or jacket-generating hydrogen peroxide, which is then detected at the electrode.] Perform the glucose analysis in the following sequence: *Negative control solution 1, Standard preparations, Assay preparations,* and *Negative control solution 2.* Determine the percentage of glucose against the *Negative control solution* for each preparation.

CALCULATIONS—

Linearity test—Use an analysis of variance (ANOVA) with one sample assayed against a standard, and using two replicates each, construct a table (see *Table 1*). Compare the value of the ratio $MSNL/MSRES_1$ to a critical value obtained from a table for an *F* distribution with $m-2$ and $3m-3$ degrees of freedom, where m is the number of dose levels for each preparation. If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity (ratio value is lower than the critical value), then proceed to the test for parallelism. If the ratio exceeds the critical value (significance level of ~~0.05),~~

•0.025),•2

the nonlinearity is statistically significant and the test is repeated, discarding the results from either the highest or lowest dose of both the *Standard preparations* and the *Assay preparations* (four dose levels). If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity, then proceed to the test for parallelism.

Table 1. ANOVA for the Rat Hepatocyte Assay for Glucagon

Source	Degrees of Freedom	SS (Sum of Squares)	MS (Mean Square)
Preparations	1	SSPREP	MSPREP
Replicates	1	SSREP	MSREP
Linear Slope	1	SSLIN	MSLIN
$Residual_3$	$4m-4$	$SSRES_3$	$MSRES_3$
Nonparallelism	1	SSNP	MSNP
$Residual_2$	$4m-5$	$SSRES_2$	$MSRES_2$
Nonlinearity	$m-2$	SSNL	MSNL
$Residual_1$	$3m-3$	$SSRES_1$	$MSRES_1$
TOTAL	$4m-1$	SST	

Parallelism test—Compare the ratio $MSNP/MSRES_2$ to a critical value obtained from an *F* distribution having 1 and $4m-5$ degrees of freedom. If the ratio $MSNP/MSRES_2$ does not indicate the presence of significant nonparallelism, then the assay is considered valid. Use the appropriate dose levels for the estimation of the relative potency.

Relative potency—Calculate the relative potency, *R,* of the *Assay preparations* as compared with the *Standard preparations* as follows.

(1) X_j is defined as the $\log_{10}$ of the j^{th} dose of the *Standard preparations* or the *Assay preparations.* The glucagon dose varies from 12.5 to 200 × 10^{-6} USP Glucagon Units per mL. For ease in the subsequent calculations, these doses are respectively represented by 1 through 5, as shown in the table below.

j	1	2	3	4	5
Dose	12.5	25	50	100	200
X_j	1.10	1.40	1.70	2.00	2.30

(2) To differentiate between the *Standard preparations* and the *Assay preparations* in the calculations, the subscript *i* will be used, with $i = 1$ to designate the *Standard preparations* and $i = 2$ to designate the *Assay preparations.* Y_{ijk} will denote the glucose concentration associated with the k^{th} replicate of the j^{th} dose of the i^{th} preparation. For example, Y_{1jk} is the glucose concentration associated with the k^{th} replicate of the j^{th} dose of the appropriate *Standard preparation;* Y_{11k} is the glucose concentration associated with the k^{th} replicate of dose 1 of the *Standard preparation;* and Y_{21k} is the glucose concentration associated with the k^{th} replicate of dose 1 of the *Assay preparation.* Dose 1 represents a glucose dose of 12.5 × 10^{-6} USP Glucagon Units per mL. Finally, Y_{132} represents the glucose concentration associated with the 2nd replicate of dose 3 for the *Standard preparation.*

(3) Y_S and Y_t denote the average glucose concentrations for the *Standard preparations* and the *Assay preparations,* respectively.

(4) Calculate the least-squares slope estimate, *b,* for a linear regression relating the Y_{ijk}'s to the X_j's as follows: $b = S_{xy}/S_{xx}$, with S_{xy} and S_{xx} calculated using the equations in *Table 2*.

(5) The log potency, *M,* is calculated using $M = -1[(Y_S - Y_t)/b]$.

(6) R = antilog *(M).*

(7) Calculate the confidence limits (upper and lower) for the relative potency, *R,* using the value $s^2 = MSRES_3$ (see *Table 1* and *Table 2*) as follows. Obtain *t* from a table for a *t* distribution having $4m-4$ degrees of freedom. For the 95% limits, the *t* values can be obtained from *Table 9* under *Design and Analysis of Biological Assays* ⟨111⟩.

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Table 2. Equations for Calculating the Sums of Squares in the Analysis of Variance*

$$Y_{i..} = \sum_{jk}\sum y_{ijk}$$

$$Y_{.j.} = \sum_{ik}\sum y_{ijk}$$

$$Y_{..k} = \sum_{ij}\sum y_{ijk}$$

$$CF = \frac{\left(\sum_{ijk}\sum\sum y_{ijk}\right)^2}{4m}$$

$$S^S_{xy} = \sum_{jk}\sum x_j y_{ijk} - \frac{\left(\sum_j x_j\right)(Y_{1..})}{m}$$

$$S^T_{xy} = \sum_{jk}\sum x_j y_{2jk} - \frac{\left(\sum_j x_j\right)(Y_{2..})}{m}$$

$$S_{xy} = S^S_{xy} + S^T_{xy}$$

$$S^S_{xx} = 2\sum_j x_j^2 - \frac{2\left(\sum_j x_j\right)^2}{m}$$

$$S^T_{xx} = S^S_{xx}$$

$$S_{xx} = S^S_{xx} + S^T_{xx}$$

$$SSPREP = \frac{\sum_i Y^2_{i..}}{2m} - CF$$

$$SSREP = \frac{\sum_k Y^2_{..k}}{2m} - CF$$

$$SSLIN = \frac{\left(S_{xy}\right)^2}{S_{xx}}$$

$$SST = \sum_{ijk}\sum\sum y^2_{ijk} - CF$$

$$SSRES_3 = SST - SSPREP - SSREP - SSLIN$$

$$SSNP = \frac{\left(S^S_{xy}\right)^2}{S^S_{xx}} + \frac{\left(S^T_{xy}\right)^2}{S^T_{xx}} - SSLIN$$

$$SSRES_2 = SSRES_3 - SSNP$$

$$SSNL = \frac{\sum_j Y^2_{.j.}}{4} - SSLIN - CF$$

$$SSRES_1 = SSRES_2 - SSNL$$

* Refer to the *Calculations* for section on *Relative Potency* for the definitions of x_j and y_{ijk}.

NOTE—For confidence limits having other probability levels (i.e., $100(1 - a)$ %), the right tail t critical value having $a/2$ area to its right is used.

Calculate $g = t^2S^2 / b^2S_{xx}$

and $F = (ts / b)\sqrt{(1/m)(1-g) + (M^2 / S_{xx})}$,

and calculate

$$M_L = (M - F)/(1 - g),$$

and

$$M_U = (M + F)/(1 - g),$$

where M is the log potency and M_L and M_U are the log potency lower and upper confidence limits. The lower and upper confidence limits for the relative potency, R, are given by

$$RL = \text{antilog}\,(M_L)$$

$$RU = \text{antilog}\,(M_U)$$

It meets the requirements if the potency is between 0.8 and 1.25 USP Glucagon Units per mg, and the confidence interval width at $P = 0.95$ does not exceed 45% of the computed potency. ■Repeat the assay if the confidence interval width exceeds 45% of the computed potency.■2S *(USP28)*

NOTES—This analysis pertains to one sample assayed against a standard, using two replicates each.

The number of dose levels for each preparation is denoted by *m*. *Table 2* gives the equations for calculating the SS terms.

In each row of the ANOVA table, the MS is obtained by dividing the SS term by the degrees of freedom.

BRIEFING

Goserelin Acetate, page 410 of *PF* 31(2) [Mar.–Apr. 2005]. On the basis of comments received, it is proposed to change the name of the test for *Identification* to *Amino acid content.* The requirements of the test have also been changed to require integration of the ^{13}C NMR signals to allow quantitation of the individual amino acids present in goserelin acetate.

(BB PP: L. Callahan) RTS—43328-1

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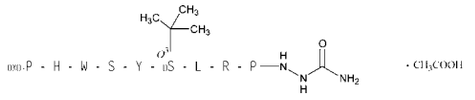
Add the following:

▲Goserelin Acetate



$C_{59}H_{84}N_{18}O_{14} \cdot xC_2H_4O_2$

Luteinizing hormone-releasing factor (pig), 6-[*O*-(1,1-dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide, acetate (salt) [*145781-92-6*].

1-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O*-*tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)-semicarbazide (Goserelin) 1269.41 [*65807-02-5*].

» Goserelin Acetate is a synthetic nonapeptide analog of the hypothalmic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate salt. It contains not less than 94.5 percent and not more than 103.0 percent of goserelin ($C_{59}H_{84}N_{18}O_{14}$), calculated on the anhydrous and acetic acid-free basis.

Packaging and storage—Preserve in a tight, light-resistant container, and store in a refrigerator.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Goserelin Acetate RS. USP Goserelin Related Compound A RS. USP Goserelin Validation Mixture RS.*

~~**Identification—**~~

~~**A:** *Nuclear Magnetic Resonance* ⟨761⟩—~~

~~*Standard solution*—Prepare a 10% w/v solution of USP Goserelin Acetate RS in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.~~

~~*Test solution*—Prepare a 10% w/v solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.~~

~~*Procedure*—Obtain a ^{13}C, proton-decoupled NMR spectrum of both the *Standard solution* and the *Test solution*. The spectra from both solutions should be qualitatively similar, and all the resonances from the spectrum of the *Standard solution* should be present in the spectrum of the *Test solution* and have the same chemical shift values; any other resonances in the spectrum of the *Test solution* should be identified.~~

~~**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 –52° and –56°.

Test solution: 2 mg per mL, in water, calculated on the anhydrous and acetic acid-free basis.

Bacterial endotoxins ⟨85⟩—It contains not more than 16 USP Endotoxin Units per mg of goserelin, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

Water, *Method I* ⟨921⟩**:** not more than 10.0%.

Limit of acetic acid—

Mobile phase—Transfer 49.04 g of sulfuric acid to a 1000-mL volumetric flask, dilute with water to volume, and mix. Accurately transfer 20 mL of this solution to a 2000-mL volumetric flask, dilute with water to volume, mix, filter, and degas.

Test solution—Dissolve about 20 mg of Goserelin Acetate, accurately weighed, in 2 to 3 mL of *Mobile phase*. Connect a 1-mL cartridge containing L44 packing to a 1-mL cartridge containing L2 packing, which is then attached to a suitable vacuum apparatus. With the vacuum applied,

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wash the cartridge combination with 2 mL of methanol followed by 15 mL of *Mobile phase,* and discard the washings. Quantitatively apply the solution containing Goserelin Acetate to the cartridge combination, and wash through the cartridge system with several small volumes of *Mobile phase*. Collect the solution and washings in a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Standard solution—Transfer 2.0 mL of glacial acetic acid to a 500-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a standard stock solution. Transfer 5.0 mL of the standard stock solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—[NOTE—Condition the column for about 24 hours until a stable baseline is obtained.] The liquid chromatograph is equipped with a 206-nm detector and a 7.8-mm × 30-cm column that contains packing L17. The column temperature is maintained at 65°, and the flow rate is about 0.8 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time is about 11 minutes for acetic acid; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3.1%.

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 percentage of acetic acid in the portion of Goserelin Acetate taken by the formula:

$$(1.049/5)(r_U / r_S)(1/W)$$

in which 1.049 is the weight per mL, in g, of glacial acetic acid; W is the sample weight of Goserelin Acetate, in g, taken to prepare the *Test solution* and corrected (for purposes of the calculation) to eliminate the water content, which is determined immediately prior to the test; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The content of acetic acid is between 4.5% and 15.0%.

Related compounds—

Mobile phase, Standard preparation, Diluted standard preparation, Resolution solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Diluted test solution—Transfer 1 mL of the *Test solution* into a 100-mL volumetric flask, and dilute with water to volume.

Procedure—Separately inject equal volumes (about 10 µL) of the *Test solution, Diluted test solution, Resolution solution,* and *System suitability solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of goserelin-related impurities in the portion of Goserelin Acetate taken by the formula:

$$r_i / r_S$$

in which r_i is the peak area response for any individual impurity in the *Test solution;* and r_S is the peak area response of the main goserelin peak in the *Diluted test solution:* not more than 1.0% of decarbamoylgoserelin is found, not more than 0.5% of any other impurity is found, and not more than 2.5% of total impurities is found.

Amino acid content, *Nuclear Magnetic Resonance* ⟨761⟩—[NOTE—Concentrations of Goserelin in both the *Standard solution* and the *Test solution* must be the same (within 5% of each other) but can be adjusted based on the quality of the ^{13}C spectrum obtained. The spectra must be acquired under the same conditions for both the *Standard solution* and the *Test solution*. The spectra obtained are of

sufficient quality to allow quantification of the integrals of the resonances specified below to be obtained. Integrals and spectra of both the *Standard solution* and the *Test solution* can be repeated and averaged.]

Standard solution—Dissolve USP Goserelin Acetate RS in deuterium oxide to obtain a known concentration of about 10% w/v, and adjust with deuterated acetic acid-d4 to a pH of 4.

Test solution—Prepare a 10% w/v solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.

Procedure—Obtain a ^{13}C, proton-decoupled NMR spectrum of both the *Standard solution* and the *Test solution*. The spectra from both solutions are qualitatively similar, and all the resonances from the spectrum of the *Standard solution* are present in the spectrum of the *Test solution* and have the same chemical shift values; identify any other resonances in the spectrum of the *Test solution.* The relative amino acid ratio between the *Standard solution* and the *Test solution* can be calculated as follows. Integrate the resonances at the approximate ppm corresponding to each amino acid in the following table.

Amino Acids	Resonances (ppm)
Azo-glycine	162.2
Histidine	118.4
Tyrosine	116.7
tert-Butyl serine	62.5
Serine	62.2
Tryptophan	55.7
Arginine	41.8
Pyroglutamic acid	26.3
Proline	26.0
Leucine	23.5

Calculate the ratio of each of the amino acids from the integrals of the *Standard solution* and the *Test solution* by the formula:

$$r_U / r_S$$

in which r_U and r_S are the integrals of the resonances of a designated amino acid obtained from the *Test solution* and the *Standard solution,* respectively. The resulting ratios fall within the following limits: histidine, tyrosine, *tert*-butyl serine, serine, tryptophan, arginine, pyroglutamic acid, proline, and leucine 0.9 to 1.1; azo-glycine 0.8 to 1.2.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (1600 : 400 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Goserelin Acetate RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Diluted standard preparation—Transfer 1 mL of the *Standard preparation* to a 10–mL volumetric flask, and dilute with water to volume.

Assay preparation—Transfer about 25 mg of Goserelin Acetate, accurately weighed, to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Resolution solution—Dissolve the contents of a vial of USP Goserelin Related Compound A RS in water to obtain a concentration of 0.1 mg per mL, and mix with an equal volume of *Diluted standard preparation.*

System suitability solution—Dissolve the contents of a vial of USP Goserelin Validation Mixture RS with 1 mL of water.

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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 3.5-µm packing L1. The column temperature is maintained between 50° and 55°, and the flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the retention time for goserelin is between 40 and 50 minutes, the relative retention times are about 0.67 for 4-D-ser-goserelin, 0.89 for decarbamoylgoserelin, 0.92 for 5-D-tyr-goserelin, 0.94 for 2-D-his-goserelin, and 1.0 for goserelin; and the resolution, *R,* between 4-D-ser-goserelin and goserelin is not less than 7.0. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* two peaks, corresponding to decarbamoylgoserelin and 2-D-his-goserelin and eluting prior to the principal peak, are visible; three peaks eluting after the principal peak are visible; the column efficiency for the principal peak is not less than 2000 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 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 goserelin ($C_{59}H_{84}N_{18}O_{14}$) in the portion of Goserelin Acetate taken (where sample weight has been corrected for water and acetic acid content, both determined immediately prior to the assay) by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Goserelin Acetate RS in the *Standard preparation;* and r_U and r_S are the goserelin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

BRIEFING

Hepatitis B Virus Vaccine Inactivated, *USP 28* page 943—See briefing under *Diphtheria Toxin for Schick Test*.

(BB VV: T. Morris) RTS—42382-2

Delete the following:

▲~~Hepatitis B Virus Vaccine Inactivated~~

~~» Hepatitis B Virus Vaccine Inactivated is a sterile preparation consisting of a suspension of particles of Hepatitis B surface antigen (HBsAg) isolated from the plasma of HBsAg carriers; treated with pepsin at pH 2, 8 M urea, and 1 : 4,000 formalin so as to inactivate any hepatitis B virus and any representative viruses from all known virus groups that may be present; purified by ultracentrifugation and biochemical procedures and standardized to a concentration of 35 µg to 55 µg of Lowry (HBsAg) protein per mL. The preparation is adsorbed on aluminum hydroxide and diluted to a concentration of 20 µg Lowry protein per mL or other appropriate concentration, depending on the intended use. The Vaccine meets the requirements for potency in animal tests using mice and by a quantitative parallel line radioimmunoassay. It contains not more than 0.62 mg of aluminum per mL and not more than 0.02 percent of residual free formaldehyde. It contains thimerosal as a preservative. It meets the requirements of the tests for pyrogen and for general safety (see *Safety Tests—General* under *Biological Reactivity Tests, In Vivo* ⟨88⟩).~~

~~**Packaging and storage**—Preserve at a temperature between 2° and 8°.~~

~~**Expiration date**—The expiration date is 3 years from the date of manufacture, the date of manufacture being the date on which the last valid potency test was initiated.~~

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~~**Labeling**—Label it to state the content of HBsAg protein per recommended dose. Label it also to state that it is to be shaken before use and that it is not to be frozen.~~ ▲*USP30*

BRIEFING

Sodium Iodide I 123 Capsules, *USP 28* page 1033. It is proposed to include in the Definition a new method of I 123 generation, proton irradiation of enriched xenon 124.

(RMI: A. Wilk) RTS—43187-3

Change to read:

» Sodium Iodide I 123 Capsules contain radioactive iodine (^{123}I) processed in the form of Sodium Iodide obtained from the bombardment of enriched tellurium 124 with protons or of enriched tellurium 122 with deuterons,

▲or by proton irradiation of enriched xenon 124,▲*USP30*

or by the decay of xenon 123 in such manner that it is carrier-free. Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{123}I as iodide expressed in megabecquerels (microcuries or millicuries) at the time indicated in the labeling. Other chemical forms of radioactivity do not exceed 5 percent of the total radioactivity. The Capsules may contain a stabilizer.

BRIEFING

Sodium Iodide I 123 Solution, *USP 28* page 1033. It is proposed to include in the Definition a new method of I 123 generation, proton irradiation of enriched xenon 124. It is also proposed to increase the radionuclidic purity limit to not less than 90% in the test for *Radionuclidic purity,* to add a requirement for solution intended for intravenous use in the test for *Bacterial endotoxins,* and to specify different pH ranges for intravenously and orally administered solutions in the *pH* section.

(RMI: A.Wilk) RTS—43187-1

Change to read:

» Sodium Iodide I 123 Solution is a solution, suitable for oral or for intravenous administration, containing radioactive iodine (^{123}I) processed in the form of Sodium Iodide, obtained from the bombardment of enriched tellurium 124 with protons or of enriched tellurium 122 with deuterons,

▲or by proton irradiation of enriched xenon 124, ▲*USP30*

or by the decay of xenon 123 in such manner that it is carrier-free.

Sodium Iodide I 123 Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{123}I as iodide expressed in megabecquerels (microcuries or millicuries) per mL at the time indicated in the labeling. Other chemical forms of radioactivity do not exceed 5 percent of the total radioactivity. The Solution may contain a preservative or stabilizer.

Change to read:

Radionuclidic purity—Using a suitable counting assembly (see *Selection of a Counting Assembly* under *Radioactivity* ⟨821⟩), determine the radionuclidic purity of the Solution: not less than ~~85.0%~~

▲90%▲*USP30*

of the total radioactivity is present as I 123.

Change to read:

Bacterial endotoxins ⟨85⟩—

▲Solution intended for intravenous use meets the requirements of the *Bacterial Endotoxins Test* ⟨85⟩; and▲*USP30*

the limit of endotoxin content is not more than 175/*V* USP Endotoxin Unit per mL of the Injection, when compared with USP Endotoxin RS, in which *V* is the maximum recommended total dose, in mL, at the expiration date or time.

Change to read:

pH ⟨791⟩: between 7.5 and 9.0

▲for solutions intended for intravenous administration; between 7.5 and 10.0 for solutions intended for oral administration.▲*USP30*

In-Process Revision

BRIEFING

Sodium Iodide I 131 Solution, *USP 28* page 1037. It is proposed to modify the *pH* section by specifying different pH ranges for intravenously and orally administered solutions.

(RMI: A. Wilk) RTS—43187-2

Change to read:

pH ⟨791⟩: between 7.5 and 9.0

▲for solutions intended for intravenous administration; between 7.5 and 10.0 for solutions intended for oral administration.▲*USP30*

BRIEFING

Diluted Isosorbide Mononitrate, page 3495 of the *Second Supplement,* and page 1060 of *PF* 31(4) [July–Aug. 2005]. It is proposed to delete the tests for *pH,Water*, and *Residue on ignition* as formulation-specific, and to make changes in the tests for *Identification, Related compounds,* and the *Assay* to accommodate different formulations.

In addition, it is proposed to revise the *USP Reference standards* section to change the name of USP Isosorbide Mononitrate RS to USP Diluted Isosorbide Mononitrate RS. Also, a *Note* is being added to identify the Reference Standards that are dry mixtures of an active component with a suitable excipient.

In the absence of any significant adverse comments, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 29-NF 24,* with an official date of April 1, 2006.

(MD-CV: E. Gonikberg) RTS—43127-1; 43132-1

Change to read:

USP Reference standards ⟨11⟩—*USP Isosorbide RS.*

•[NOTE—The following Reference Standards are dry mixtures of an active component with suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.]•2
USP Diluted Isosorbide Dinitrate RS. USP

•*Diluted*•2
Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS.

Change to read:

Identification—

A: ~~*Infrared Absorption* ⟨197K⟩.~~

•Shake a quantity of it, equivalent to about 25 mg of isosorbide mononitrate, with 10 mL of acetone for 5 minutes. Filter, evaporate to dryness at a temperature below 40°, and dry the residue in a vacuum over phosphorus pentoxide for 16 hours: the IR absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation from the residue obtained from USP Diluted Isosorbide Mononitrate RS.•2

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:

~~•**pH** ⟨791⟩: between 4.8~~

~~■4.0■2S *(USP29)*~~
~~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.•2~~

Delete the following:

~~•**Water,** *Method Ic* ⟨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.•2~~

In-Process Revision

Delete the following:

•**~~Residue on ignition~~** ⟨~~281~~⟩: ~~not more than 0.1%.~~
~~*Caution—Material is explosive upon heating; digest the sample thoroughly before ignition.*~~•2

Change to read:

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 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

•Diluted•2
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~~

•isosorbide mononitrate•2
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:

~~$5556(C/W)(r_U/r_S)$~~

•$100(CV/W)(r_U/r_S)$•2

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,~~

•isosorbide mononitrate related compound A or isosorbide dinitrate, as appropriate,•2
in the *Standard solution; W* is the ~~weight, in mg,~~

•amount, in mg, of isosorbide mononitrate in the portion•2
of Diluted Isosorbide Mononitrate used to prepare the *Test solution*,

•based on the label claim; V is the volume, in mL, of the *Test solution;*•2
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.

Change to read:

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

•Diluted•2

In-Process Revision

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

•of isosorbide mononitrate•2
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,~~

•an accurately weighed amount of Diluted Isosorbide Mononitrate, equivalent to 100 mg of isosorbide mononitrate,•2
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:

~~$50C(r_U / r_S)$~~

•$CV(r_U / r_S)$•2

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;*

•V is the volume, in mL, of the *Assay preparation;*•2
and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ivermectin, *USP 28* page 1093 and page 3250 of the *First Supplement.* On the basis of comments received, it is proposed to change the test conditions and the *Test solution* in the test for *Specific rotation.* In the test for *Limit of alcohol and formamide,* it is proposed to change the preparation of *Standard solutions 1, 3,* and *4* and the preparation of the *Test solution;* and to make changes in the *Chromatographic system* and the *Procedure.*

(VET DRUG: I. DeVeau) RTS—41834-1

Change to read:

Specific rotation ⟨781S⟩**:** between –17° and –20°

▲measured at 20°,▲*USP30*
calculated on the water-, alcohol-, and formamide-free basis.

Test solution: ~~5~~

▲25▲*USP30*
mg per mL, in methanol.

Change to read:

Limit of alcohol and formamide—

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

▲▲*USP30*
Standard solution 1—Transfer ~~2.0~~

▲3.0▲*USP30*
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 0.002 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 0.0008 mL of alcohol and 0.0004 mL of formamide.~~

▲Transfer 3.0 mL of *Standard solution 1* and 3.0 mL of *Standard solution 2* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of 0.0009 and 0.0003 mL per mL, respectively. Transfer 4.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove and discard the upper *m*-xylene layer.▲*USP30*

In-Process Revision

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 0.004 and 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 0.0016 mL of alcohol and 0.0008 mL of formamide.~~

▲Transfer 8.0 mL of *Standard solution 1* and 8.0 mL of *Standard solution 2* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of 0.0024 and 0.0008 mL per mL, respectively. Transfer 4.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove and discard the upper *m*-xylene layer.▲*USP30*

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.~~

▲Transfer 0.12 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, and mix well. [NOTE—If the solution is hazy, warm slightly (to a temperature of 40° to 50°) while mixing, and centrifuge.] Transfer the *m*-xylene layer to another 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, centrifuge, and discard any remaining *m*-xylene.▲*USP30*

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 ■10 : 1■*IS (USP28)* 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, 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 ■220°.■*IS (USP28)* and the detector temperature is maintained at about ■280°.■*IS (USP28)*~~

▲The gas chromatograph is equipped with a flame-ionization detector and contains a 3.2-mm × 1.8-m column of either stainless steel or glass, packed with 80–100 mesh support S2. The carrier gas is helium or nitrogen, flowing at a rate of approximately 40 mL per minute. The chromatograph is programmed as follows. The column temperature is maintained at about 140° for 4 minutes after injection, then increased at a rate of 20° per minute to 180° and maintained at 180° for 15 minutes. The injection port temperature is maintained at about 190°, and the detector temperature is maintained at about 250°.▲*USP30*

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 are found~~

▲alcohol and formamide. Prepare calibration plots for alcohol and formamide by plotting peak area versus solvent concentration, in mL per mL, for each *Standard solution* used. Use these plots to obtain the alcohol and formamide concentration in the *Test solution*. [NOTE—If the response of the alcohol or formamide peak in the *Test solution* is outside the ranges of the peak responses obtained for *Standard solution 3* and *Standard solution 4*, prepare additional *Standard solutions* of suitable concentration, 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:

$$400CD/W$$

In-Process Revision

in which *C* is the concentration, in mL per mL, of alcohol or formamide, as appropriate, in the *Test solution; D* is the density of alcohol (0.79 g per mL) or formamide (1.13 g per mL); and *W* is the weight, in g, of Ivermectin taken: not more than 5.0% of alcohol and 3.0% of formamide are found.▲*USP30*

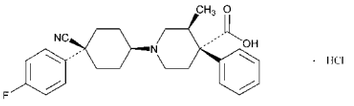
BRIEFING

Levocabastine Hydrochloride. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on the *Levocabastine Hydrochloride* monograph in the *European Pharmacopoeia 5.0,* is being proposed.

(PA1: K. Russo) RTS—43014-1

Add the following:

▲Levocabastine Hydrochloride



$C_{26}H_{29}FN_2O_2 \cdot HCl$ 456.98

4-Piperidinecarboxylic acid, 1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-, monohydrochloride, (–)-[1(*cis*),3α,4β]-.

(–)-*trans*-1-[*cis*-4-Cyano-4-(*p*-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid monohydrochloride [*79547-78-7*].

» Levocabastine Hydrochloride contains not less than 98.5 percent and not more than 101.5 percent of $C_{26}H_{29}FN_2O_2 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Protect from light.

USP Reference standards ⟨11⟩—*USP Levocabastine Hydrochloride RS. USP Levocabastine Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the tests for *Chloride* ⟨191⟩.

C: It meets the requirement for *Specific rotation* ⟨781S⟩.

Specific rotation ⟨781S⟩**:** between –102° and –106° at 20°.

Test solution: 10 mg per mL, in methanol.

Loss on drying ⟨731⟩—Dry about 1.000 g of sample at 105° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%, based on a sample weight of about 1.000 g.

Related compounds—[NOTE—Prepare solutions immediately before use.]

Diluent—Prepare an aqueous solution containing about 2 mg per mL of sodium hydroxide.

pH 9.0 Buffer—Dissolve about 1.39 g of boric acid in water, and adjust with 1 N sodium hydroxide to a pH of 9.0. Dilute with water to 100 mL.

Run buffer—Dissolve about 1.08 g of sodium dodecyl sulfate and about 650 mg of hydroxypropyl-β-cyclodextrin in 5 mL of isopropyl alcohol, then dilute with *pH 9.0 Buffer* to 50 mL.

In-Process Revision

System suitability solution—Dissolve suitable quantities of USP Levocabastine Hydrochloride RS and USP Levocabastine Related Compound A RS in *Diluent* to obtain a solution containing about 0.0125 mg per mL of each compound.

Standard solution—Dilute 5.0 mL of the *Test solution* with *Diluent* to 100 mL. Dilute 1.0 mL of this solution with *Diluent* to 10 mL to obtain a solution containing about 0.0125 mg of levocabastine hydrochloride per mL.

Test solution—Transfer about 25 mg of Levocabastine Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

System setup (see *Capillary Electrophoresis* ⟨727⟩)—The capillary electrophoresis system is equipped with a 214-nm detector and a 75-µm × 50-cm uncoated fused-silica capillary column. The temperature is maintained at 50°. The current is programmed as follows.

Time (minutes)	Current (µA)
0–0.17	0→75
0.17–15	75→130
15–40	130
40–60	130→200

Equilibrate the capillary column with the *Diluent* for 2 minutes, then equilibrate with the *Run buffer* for at least 5 minutes. Inject the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative migration times are approximately 1.07 for levocabastine related compound A and 1.0 for levocabastine; the resolution, *R*, between levocabastine and levocabastine related compound A is not less than 4. If necessary, adjust the current gradient to achieve the required resolution.

Procedure—Separately inject equal volumes (pressure of 3450 Pa for 5 seconds) of the *Diluent* (as the blank), the *Standard solution,* and the *Test solution,* and record the peak responses: the area for any peak in the *Test solution,* other than the major peak, is not greater than the major peak area obtained from the *Standard solution* (0.5%); and the sum of all peak areas in the *Test solution,* except for the major peak, is not greater than twice the major peak area obtained from the *Standard solution* (1.0%). Disregard any peak originating from the *Diluent*. Disregard any peak with an area of less than 0.1 times the major peak area obtained from the *Standard solution* (0.05%).

Assay—Dissolve about 175 mg of Levocabastine Hydrochloride, accurately weighed, in 50 mL of alcohol, and add 5.0 mL of 0.01 N hydrochloric acid. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. The volume of titrant required to titrate Levocabastine Hydrochloride is the difference between the first and third endpoints. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N sodium hydroxide VS is equivalent to 22.85 mg of $C_{26}H_{29}FN_2O_2 \cdot HCl$. ▲*USP30*

BRIEFING

Lindane, *USP 28* page 1136. It is proposed to replace the nonspecific titration method in the *Assay* with a more selective gas chromatographic method. The analysis is performed with a J&W Scientific fused-silica column coated with a 1-µm phase G46.

(PA7b: B. Davani) RTS—43022-1

In-Process Revision

Change to read:

» Lindane is the gamma isomer of hexachlorocyclohexane. It contains not less than 99.0 percent and not more than ~~100.5~~

▲101.0▲*USP30*
percent of lindane (γ-$C_6H_6Cl_6$).

Change to read:

Assay— ~~Transfer about 400 mg of Lindane, accurately weighed, to a wide-mouth, glass-stoppered, 250-mL conical flask, add 20 mL of alcohol, and warm on a steam bath until solution is complete. Cool, add 20 mL of a 1 in 20 solution of potassium hydroxide in alcohol, swirl gently, and allow to stand for 10 minutes. Dilute with water to about 100 mL, neutralize with 2 N nitric acid, and add 5 mL in excess. Pipet into the solution 50 mL of 0.1 N silver nitrate VS, then add 5 mL of nitrobenzene, and shake vigorously. Add ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 0.1 N silver nitrate is equivalent to 9.694 mg of $C_6H_6Cl_6$.~~

▲*Internal standard solution*—Dissolve *n*-octadecane in methylene chloride to obtain a solution having a concentration of about 0.5 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Lindane RS in *Internal standard solution* to obtain a solution having a known concentration of about 2 mg per mL.

System suitability solution—Prepare solutions of α-benzene hexachlorides (BHC) at 1000 µg per mL of methanol, *β*-BHC at 1000 µg per mL of acetone, and *δ*-BHC at 1000 µg per mL of methanol. Transfer 100 µL each of α- BHC, *β*-BHC and *δ*-BHC solutions to a 4-mL conical vial, and evaporate under a stream of nitrogen to dryness. Add to the vial a 100-µL aliquot of the *Standard preparation*. Insert the stopper, and shake vigorously to dissolve the residue.

Assay preparation—Transfer about 10 mg of Lindane, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with methylene chloride to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused-silica column coated with a 1-µm phase G46. The chromatograph is programmed as follows. The initial column temperature is maintained at 120° for 1 minute. Then, the temperature is increased at a rate of 20° per minute to 150°, and then ramped at a rate of 10° per minute to 280° and maintained at that temperature for 4 minutes. The injection port and detector temperatures are maintained at 300°. The injection split ratio is 50 : 1. Chromatograph the *Standard preparation* and the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times for *n*-octadecane and lindane are about 0.85 and 1.0, respectively. [NOTE—Typical retention times for α-BHC, *β*-BHC, γ-BHC, *δ*-BHC, and *n*-octadecane are 15.7, 17.8, 16.5, 18.8, and 13.9 minutes, respectively.] The resolution, *R,* between *n*-octadecane and α-BHC is not less than 21, between lindane (γ-BHC) and α-BHC is not less than 9, between *β*-BHC and lindane is not less than 14, and between *δ*-BHC and *β*-BHC is not less than 8; the tailing factors for *n*-octadecane and lindane are less than 1.5 and 1.2, respectively; and the relative standard deviation of the ratios of peak area responses of lindane to *n*-octadecane for replicate injections of *Standard preparation* is not more than 1.5%.

Procedure—Separately inject equal volumes (about 1 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 γ-$C_6H_6Cl_6$ in the portion of Lindane taken by the formula:

$$5C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Lindane RS in the *Standard preparation;* and R_U and R_S are the ratios of the peak responses of lindane to *n*-octadecane, obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Mangafodipir Trisodium, *USP 28* page 1178 and page 3502 of the *Second Supplement.* On the basis of comments received, it is proposed to specify the *Standard solution* used to determine the relative standard deviation for replicate injections in the test for *Limit of residual solvents.*

(RMI: A. Wilk) RTS—43133-1

Change to read:

Limit of residual solvents—

Internal standard solution—Transfer 600 µL of methyl ethyl ketone to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a concentration of about 5 mg per mL. Transfer 2 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard stock solution—Transfer about 1 g of dehydrated alcohol and 1 g of acetone, both accurately weighed, to a 100-mL volumetric flask, and dilute with water to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about 1 mg each of alcohol and acetone per mL.

Standard solutions—Transfer 10.0 mL of *Internal standard solution* to each of four 100-mL volumetric flasks. Separately add 0 mL, 1.0 mL, 5.0 mL, and 10.0 mL of *Standard stock solution* to the volumetric flasks, and dilute each with water to volume to obtain solutions having known concentrations of 0.0 µg per mL and about 10 µg per mL, 50 µg per mL, and 100 µg per mL each of alcohol and acetone, respectively. Add 7.0 mL of each *Standard solution* to separate headspace sample vials, and cap.

Test solution—Transfer about 1 g of Mangafodipir Trisodium, accurately weighed, to a sample vial, add 7.0 mL of the *Standard solution* having a concentration of 0.0 µg per mL, cap, and swirl to dissolve.

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 1.8-µm G43 stationary phase. The carrier gas is helium, flowing at a rate of 1.5 mL per minute. The temperatures of the injection port and the oven are maintained at 150° and 50°, respectively. The bath temperature for the headspace sample vials is maintained at 90°, the valve/loop temperature is maintained at 130°, and the sample thermostating time is 15 minutes. Chromatograph the *Standard solutions,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between alcohol and acetone is not less than 5; and the relative standard deviation for replicate injections

▲of the *Standard solution* having a concentration of 100 µg per mL,▲*USP30*
determined from the peak response ratios of the analyte to the internal standard, is not more than 2.0%. Calculate the peak response ratios of the analyte to the internal standard, and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient. A suitable system is one that yields a line having a correlation coefficient of not less than 0.990.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspace of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentages (w/w) of alcohol and acetone in the portion of Mangafodipir Trisodium taken by the formula:

$$(7/10{,}000)(C/W)$$

in which C is the concentration, in µg per mL, of alcohol or acetone in the *Test solution,* as determined from the relevant standard response line; and W is the weight, in g, of Mangafodipir Trisodium taken: not more than 0.1% of alcohol is found; and not more than 0.01% of acetone is found, both calculated on the anhydrous basis.

BRIEFING

Mirtazapine, page 3257 of the *First Supplement.* On the basis of data received, it is proposed to change the currently required *Method I* in the test for *Heavy metals* to *Method II.*

(MD-PP: R. Ravichandran) RTS—42658-1

Change to read:

Heavy metals, ~~*Method I*~~

▲*Method II*▲*USP30*
⟨231⟩: 0.001%

~~*Diluent:* a mixture of methanol and water (85 : 15).~~

~~*Test preparation*—Dissolve 4.8 g of mirtazapine in 51 mL of methanol. Add 9 mL of water. Adjust 25 mL of this solution with 1 N acetic acid to a pH of between 3.0 and 4.0, using a short range pH indicator paper as the internal indicator. Dilute with *Diluent* to 40 mL, and mix.~~

~~NOTE—Use *Diluent* instead of water to prepare the *Standard Preparation* and *Monitor Preparation.* Prepare a blank of *Diluent,* and use *Diluent* instead of water in the *Procedure.*~~

▲*Test preparation*—Use a weighed quantity, approximately 4.0 g, of Mirtazapine.▲*USP30*

In-Process Revision

BRIEFING

Ondansetron Injection, *USP 28* page 1420. It is proposed to specify that the total impurity acceptance criteria include the results from the test for *Limit of ondansetron related compound D* and the results from the test for *Chromatographic purity.* Also, the redundant section for *Standard solution* preparation in the test for *Chromatographic purity* has been deleted since it is not required for the test.

(MD-PP: R. Ravichandran) RTS—43204-1

Change to read:

Chromatographic purity—

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

~~*Standard solution*—Proceed as directed for *Standard preparation* in the *Assay.*~~

▲▲*USP30*

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 volume of Injection 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

▲including ondansetron related compound D from the test for *Limit of ondansetron related compound D*▲*USP30* is not more than 0.5%.

BRIEFING

Orphenadrine Citrate Injection, *USP 28* page 1423. On the basis of comments received regarding the stability of the *Assay preparation* dissolved in *Mobile phase,* in the *Assay* it is proposed to change the diluent used to prepare the *Standard preparation,* the *System sensitivity solution,* and the *Assay preparation* from *Mobile phase* to water to improve the stability of the preparations.

(MD-PP: R. Ravichandran) RTS—42433-1

Change to read:

Assay—

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,*~~

▲water,▲*USP30*
and dilute quantitatively, and stepwise if necessary, with ~~*Mobile phase*~~

▲water▲*USP30*
to obtain a solution having a known concentration of about 0.9 mg per mL.

System sensitivity solution—Dilute a volume of the *Standard preparation* quantitatively, and stepwise if necessary, with ~~*Mobile phase*~~

▲water▲*USP30*
to obtain a solution having a known concentration of about 0.00045 mg per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 90 mg of orphenadrine citrate, to a 100-mL volumetric flask, dilute with ~~*Mobile phase*~~

▲water▲*USP30*
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 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 peak areas for orphenadrine citrate. Calculate the quantity, in mg, of orphenadrine citrate ($C_{18}H_{23}NO \cdot C_6H_8O_7$) in each mL of the Injection taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard preparation; V* is the volume, in mL, of Injection taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Oxybutynin Chloride Extended-Release Tablets, page 1276 of *PF* 30(4) [July–Aug. 2004]. It is proposed to modify the system suitability requirements in the test for *Related compounds* and in the *Assay.* It is also proposed to change the *Tolerances* in the *Drug release* test to conform to those approved by the FDA for this product. In addition, it is proposed to modify the *Packaging and storage* statement to indicate storage at controlled room temperature.

(BPC: M. Marques; PA4: E. Gonikberg) RTS—43085-1; 43226-1

Add the following:

▲Oxybutynin Chloride Extended-Release Tablets

» Oxybutynin Chloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$).

Packaging and storage—Preserve in tight containers. Store at ~~25°, excursions permitted between 15° and 30°.~~ controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Oxybutynin Chloride RS. USP Oxybutynin Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197⟩—

Test specimen—Add a quantity of finely powdered Tablets, equivalent to about 15 mg of oxybutynin chloride, to 5 mL of water per Tablet. Mix for 1 minute. Adjust with 0.1 N sodium hydroxide to a pH between 7 and 8. Extract the solution twice with 10 mL of ether. Combine the extracts, evaporate the ether, and dry under vacuum over silica gel for at least 30 minutes. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.

Standard specimen—Dissolve 15 mg of USP Oxybutynin Chloride RS in 5 mL of water. Proceed as directed for the *Test specimen,* beginning with "Adjust with".

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⟩**—**

Medium: simulated gastric fluid without enzymes; 50 mL.

Apparatus 7: 30 cycles per minute; 2- to 3-cm amplitude.

Times: 4, 10, and 24 hours.

Determine the amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved by employing the following method.

0.035 M Phosphate buffer, pH 2.2—Dissolve about 4.83 g of monobasic sodium phosphate in 1000 mL of water, add 2.3 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.2 ± 0.2.

Acidified water—To 1 L of water add phosphoric acid dropwise to a pH of 3.5, and mix well.

Standard stock solutions—Dissolve accurately weighed quantities of USP Oxybutynin RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain solutions having known concentrations of about 250, 300, and 350 µg per mL.

Standard solutions—Prepare a series of dilutions of the *Standard stock solutions* in acidified water having final concentrations similar to those expected in the *Test solution.*

Test solution—Use portions of the solution under test. If the solution is cloudy, centrifuge at 2000 rpm for 10 minutes, and use the supernatant.

In-Process Revision

Mobile phase—Prepare a suitable filtered and degassed mixture of *0.035 M Phosphate buffer, pH 2.2* and acetonitrile (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Use a medium range *Standard solution* of USP Oxybutynin Chloride RS.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 5-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at about 35°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the tailing factor is greater than 0.5 and less than 2.5; 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 solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Construct a calibration curve by plotting the peak response versus concentration of the *Standard solutions.* A weighing factor, $1/x$, is applied to the regression line of the calibration curve to enhance the accuracy of the low standard concentrations. Determine the amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved in each interval from a linear regression analysis of the calibration curve.

Tolerances—The percentages of the labeled amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

FOR TABLETS LABELED TO CONTAIN 5 MG OR 10 MG OF OXYBUTYNIN CHLORIDE:

Time (hours)	Amount dissolved
4	not more than 20%
10	between 34.5% and 59.5%
24	not less than 80%

FOR TABLETS LABELED TO CONTAIN 15 MG OF OXYBUTYNIN CHLORIDE:

Time (hours)	Amount dissolved
4	not more than 20%
10	between 34.5% and 59.5%
24	not less than 75%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Mobile phase, Diluent, Preparation medium, Impurity stock solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Impurity standard solution—Dilute the *Impurity stock solution* with *Diluent* to obtain a solution having a known concentration of about 1 µg of oxybutynin related compound A per mL. [NOTE—Oxybutynin related compound A is phenylcyclohexylglycolic acid.]

Test solution—Use the *Assay preparation*.

~~*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 L11. The flow rate is about 1.5 mL per minute. Chromatograph the *Impurity standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is greater than 0.75 and not more than 2.5 for the phenylcyclohexylglycolic acid peak. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, *R,* between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5; and the relative standard deviation of peak area responses for six replicate injections of *System suitability solution* is not more than 3% for each compound.~~

In-Process Revision

Procedure—Separately inject equal volumes (about 50 µL) of the *Impurity 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 Tablets taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of oxybutynin related compound A in the *Impurity standard solution;* and r_U and r_S are the peak responses for each impurity obtained from the *Test solution* and the *Impurity standard solution,* respectively. Disregard any peak less than 0.1%: not more than 1% of oxybutynin related compound A is found, and not more than 2% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, and triethylamine (65 : 35 : 0.15). Adjust with phosphoric acid to a pH of 3.9, degas, and filter.

Diluent—Use water adjusted with phosphoric acid to a pH of 3.5.

Preparation medium—Prepare a solution of methanol and acetonitrile (1 : 1).

Impurity stock solution—Dissolve an accurately weighed quantity of USP Oxybutynin Related Compound A RS in acetonitrile to obtain a solution having a known concentration of about 0.11 mg per mL.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in acetonitrile to obtain a solution having a known concentration of about 0.37 mg per mL.

System suitability solution—Transfer 10 mL of the *Standard stock preparation* and 1 mL of the *Impurity stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard preparation—Dilute the *Standard stock preparation* with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—

FOR TABLETS THAT CONTAIN 5 MG OF OXYBUTYNIN CHLORIDE—Place 10 Tablets in a 500-mL volumetric flask, add 150 mL of *Preparation medium,* and stir ~~overnight~~ for at least 4 hours or until dissolved. Dilute with *Diluent* to volume. Mix thoroughly, centrifuge, and use the clear supernatant.

FOR TABLETS THAT CONTAIN 10 MG OF OXYBUTYNIN CHLORIDE OR MORE—Place 10 Tablets in a 1000-mL volumetric flask, add 300 mL of *Preparation medium,* and stir ~~overnight~~ for at least 4 hours or until dissolved. Dilute with *Diluent* to volume. If necessary, make a further dilution with *Diluent* to obtain a solution having a final concentration equivalent to 0.1 mg per mL of oxybutynin chloride. Mix thoroughly, centrifuge, and use the clear supernatant.

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 L11. 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 greater than 0.75 and not more than 2.5.~~ Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for oxybutynin and about 1.6 for oxybutynin related compound A; the resolution, *R,* between oxybutynin and oxybutynin related compound A is not less than 1.5; the tailing factor is greater than 0.75 and not more than 2.5 for each peak; and the relative standard deviation of peak area responses for six replicate injections is not more than 3% for each compound.

In-Process Revision

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 area responses for the major peaks. Calculate the quantity, in mg, of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) in the portion of Tablets taken by the formula:

$$CVD(r_U / r_S)$$

in which C is the concentration, in mg per mL, of oxybutynin chloride in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation; D* is the dilution factor; and r_U and r_S are the peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Prednicarbate Cream; Prednicarbate Ointment. Because there are no existing *USP* monographs for these drug products, new monographs are being proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the Symmetry brand of L1 column. The typical retention time is about 38.2 minutes for prednicarbate.

(PA1: C. Anthony) RTS—42987-1

Add the following:

▲Prednicarbate Cream

» Prednicarbate Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of prednicarbate ($C_{27}H_{36}O_8$). It may contain a suitable preservative.

Packaging and storage—Preserve in tight, light-resistant containers at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Prednicarbate RS.*

Identification—The retention time of the prednicarbate 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 3.5 and 5.0, in a solution prepared in the following manner. Add 15 mL of boiling water to 3.5 g of cream in a 50-mL centrifuge tube, and shake vigorously until an emulsion is formed. Loosen the cap, and place in a steam bath for 5 minutes. Centrifuge the hot solution. After cooling to room temperature, collect the lower aqueous solution in a glass tube, and determine the pH.

Consistency—At room temperature, a cream string having a length of 2 cm retains its shape on a glass plate for at least 10 minutes. It can easily be spread and has no visible lumps.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic bacterial count does not exceed 100 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

In-Process Revision

Related compounds—

Solution A, Solution B, Mobile phase, Standard stock solution, Resolution solution, Solution 1, and *Solution 2*—Prepare as directed in the *Assay.*

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

System sensitivity solution—Dilute 1.0 mL of the *Standard solution* with dehydrated alcohol to 50.0 mL. Dilute 1.0 mL of the solution thus obtained with *Solution A* to 20.0 mL.

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

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *System sensitivity solution:* the signal-to-noise ratio is not less than 3. Chromatograph the *Test solution,* and record the responses of all the peaks other than the prednicarbate peak, as directed for *Procedure:* the relative retention times are about 0.57 for prednisolone-17-ethylcarbonate, 0.64 for prednisolone-21-propionate, 1.0 for prednicarbate, and 1.04 for 1,2-dihydroprednicarbate.

Procedure—Inject a volume (about 60 µL) of *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound and unknown impurity in the portion of Cream taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each individual impurity obtained from the *Test solution,* and r_s is the sum of all peak responses obtained from the *Test solution:* not more than 2.0% of prednisolone-17-ethylcarbonate and prednisolone-21-propionate is found; not more than 0.1% of any individual related compound is found; and not more than 5.0% of total related compounds is found.

Assay—

Solution A—Prepare a 0.01 M solution of potassium dihydrogen phosphate in water.

Solution B—Prepare a mixture of acetonitrile and dehydrated alcohol (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⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Prednicarbate RS in dehydrated alcohol, and dilute quantitatively and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of 0.3 mg per mL.

Standard preparation—Transfer 10.0 mL of *Standard stock preparation* to a 100-mL volumetric flask, add 15 mL of tetrahydrofuran and 30 mL of *Solution B,* and dilute with *Solution A* to volume.

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 3.0 mg of prednicarbate to a 100-mL volumetric flask. Add 15 mL of tetrahydrofuran, shake vigorously, and allow to stand in an ultrasonic bath until the sample has dissolved. Add 20 mL of dehydrated alcohol, and shake vigorously. Add 20 mL of acetonitrile, and shake vigorously. Immediately dilute with *Solution A* to volume, and shake vigorously. Allow to stand in an ice bath for at least 15 minutes. Shake the samples vigorously, and pass through a folded paper filter. Pass the filtrate through a 0.45-µm membrane filter.

Solution 1—Transfer about 15 mg each of prednisolone-17-ethylcarbonate and prednisolone-21-propionate, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with dehydrated alcohol to volume.

Solution 2—Transfer about 15 mg of 1,2-dihydroprednicarbate, accurately weighed, to a 50-mL volumetric flask, add 1.0 mL of *Solution 1,* and dilute with dehydrated alcohol to volume.

Resolution solution—Transfer 10.0 mL of the *Standard preparation* to a volumetric flask, add 1.0 mL of *Solution 2,* 1 mL of tetrahydrofuran, and 2 mL of acetonitrile, and dilute with *Solution A* to 20.0 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 243-nm detector and a 4.0-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	67	33	equilibration
5–45	67→40	33→60	linear gradient
45–50	40	60	isocratic
50–55	40→20	60→80	linear gradient
55–70	20	80	isocratic
70–75	20→67	80→33	linear gradient
75–85	67	33	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between prednicarbate and 1,2-dihydroprednicarbate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the prednicarbate peak is between 0.7 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 60 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 prednicarbate ($C_{27}H_{36}O_8$) in each g of Cream taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Prednicarbate RS in the *Standard preparation; W* is the weight, in g, of Cream taken; and r_U and r_S are the prednicarbate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Prednicarbate Ointment—See briefing under *Prednicarbate Cream*.

(PA1: C. Anthony) RTS—43000-1

Add the following:

▲Prednicarbate Ointment

» Prednicarbate Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of prednicarbate ($C_{27}H_{36}O_8$), in a suitable ointment base.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

In-Process Revision

USP Reference standards ⟨11⟩—*USP Prednicarbate RS.*

Identification—It meets the requirements of the *Identification* test under *Prednicarbate Cream*.

Consistency—At room temperature, an ointment string having a length of 2 cm retains its shape on a glass plate for at least 10 minutes. It can easily be spread and has no visible lumps.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic bacterial count does not exceed 100 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

Related compounds—

Solution A, Solution B, Mobile phase, Standard stock solution, Resolution solution, Solution 1, and *Solution 2*—Prepare as directed in the *Assay* under *Prednicarbate Cream.*

System sensitivity solution—Prepare as directed for *Related compounds* under *Prednicarbate Cream*.

Test solution—Prepare as directed for the *Assay preparation* under *Prednicarbate Cream*.

Chromatographic system—Prepare as directed in the *Assay* under *Prednicarbate Cream*. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 3. Chromatograph the *Test solution,* and record the responses of all the peaks other than the prednicarbate peak, as directed for *Procedure:* the relative retention times are about 0.57 for prednisolone-17-ethylcarbonate, 0.64 for prednisolone-21-propionate, 1.0 for prednicarbate, and 1.04 for 1,2-dihydroprednicarbate.

Procedure—Inject a volume (about 60 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound and unknown impurity in the portion of Ointment 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 all the peak responses obtained from the *Test solution:* not more than 2.0% of prednisolone-17-ethylcarbonate and prednisolone-21-propionate is found; not more than 0.1% of any individual related compound is found; and not more than 5.0% of total related compounds is found.

Assay—

Solution A, Solution B, Mobile phase, Standard stock preparation, Standard preparation, Assay preparation, Solution 1, Solution 2, and *Resolution solution*—Prepare as directed in the *Assay* under *Prednicarbate Cream*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 243-nm detector and a 4.0-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	67	33	equilibration
5–45	67→40	33→60	linear gradient
45–50	40	60	isocratic
50–55	40→20	60→80	linear gradient
55–70	20	80	isocratic
70–75	20→67	80→33	linear gradient
75–85	67	33	isocratic

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Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between prednicarbate and 1,2-dihydroprednicarbate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the prednicarbate peak is between 0.7 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 60 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 prednicarbate ($C_{27}H_{36}O_8$) in each g of Ointment taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Prednicarbate RS in the *Standard preparation; W* is the weight, in g, of Ointment taken; and r_U and r_S are the prednicarbate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

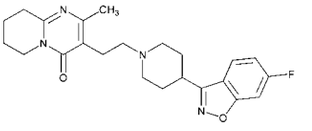
BRIEFING

Risperidone. Because there is no existing *USP* monograph for this active drug substance, a new monograph is being proposed. The proposed liquid chromatographic tests for *Related compounds* and the *Assay* are based on analyses performed with the Hypersil BDS C18 (L1) column. The typical retention time for risperidone is about 9.5 minutes. The test for *Residual solvents* reflects the change in general chapter ⟨467⟩ title from *Organic Volatile Impurities* to *Residual Solvents* and the adoption of the ICH guidelines in the chapter, as proposed in *PF* 31(5) [Sept.–Oct. 2005].

(MD-PP: R. Ravichandran) RTS—42740-1

Add the following:

▲Risperidone



$C_{23}H_{27}FN_4O_2$ 410.48

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-.

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one [*106266-06-2*].

» Risperidone contains not less than 98.0 percent and not more than 102.0 percent of $C_{23}H_{27}FN_4O_2$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

USP Reference standards ⟨11⟩**—***USP Risperidone RS. USP Risperidone System Suitability Mixture RS.* [NOTE—This mixture contains risperidone, *Z*-oxime, 9-hydroxyrisperidone, and 6-methylrisperidone.]

In-Process Revision

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.*

Loss on drying ⟨731⟩—Dry in vacuum at 80° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%, a 2.0-g test specimen being used.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Related compounds—

Buffer solution, Solution A, Solution B, Mobile phase, Diluent, System suitability 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 *Assay preparation*.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatogram. Identify the impurities based on the relative retention times given in *Table 1,* and measure the peak responses. Calculate the percentage of each risperidone related compound in the portion of Risperidone taken by the formula:

$$100(C_S/C_U)(r_U/r_S)(1/F)$$

in which C_S and C_U are the concentrations, in mg per mL, of risperidone in the *Standard solution* and the *Test solution* respectively; r_U is the peak area of each impurity obtained from the *Test solution;* r_S is the peak area of risperidone obtained from the *Standard solution;* and F is the relative response factor for each impurity relative to risperidone. In addition to not exceeding the limits in *Table 1,* not more than 0.10% of any unknown impurity (use F value of 1.0) is found and not more than 0.30% of the total impurities is found. Disregard the impurity peaks that are less than 0.05%.

Table 1

Related Compound	Relative Retention Time (RRT)	Relative Response Factor (*F*)	Limit (%)
E-oxime[1]	0.60	1.0	NMT 0.20
Z-oxime[2]	0.67	0.63	NMT 0.20
9-hydroxyrisperidone[3]	0.76	0.92	NMT 0.20
5-fluororisperidone[4]	0.94	1.0	NMT 0.20
Risperidone	1.0	1.0	—
6-methylrisperidone[5]	1.2	0.95	NMT 0.20

[1] 3-[2-[4-[*(E)*-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one
[2] 3-[2-[4-[*(Z)*-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one
[3] (9*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one
[4] 3-[2-[4-(5-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one
[5] (6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

Residual solvents ⟨467⟩**:** meets the requirements.

Assay—

Buffer solution—Dissolve 15.4 g of ammonium acetate in 1 L of water. Adjust with 10% acetic acid to a pH of 6.5, and mix.

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Solution A—Mix 100 mL of *Buffer solution* with 150 mL of methanol in a 1000-mL volumetric flask, and dilute with water to volume.

Solution B—Mix 100 mL of *Buffer solution* with 850 mL of methanol in a 1000-mL volumetric flask, and dilute with water to volume.

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—Mix 100 mL of *Buffer solution* with 900 mL of water and 1000 mL of methanol.

System suitability solution—Prepare a 1 mg per mL solution of USP Risperidone System Suitability Mixture RS in *Diluent*.

Standard preparation—Dissolve an accurately weighed quantity of USP Risperidone RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Risperidone in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a concentration of about 1.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–1	70	30	isocratic
1–20	70→5	30→95	linear gradient
20–25	5	95	isocratic
25–27	5→70	95→30	linear gradient
27–35	70	30	re-equilbration

Inject the *System suitability solution*. Record the peak responses as directed for *Procedure,* and identify the peaks due to *Z*-oxime, 9-hydroxyrisperidone, 6-methylrisperidone, and risperidone using the relative retention times (RRT) from *Table 1*; the resolution, *R,* between *Z*-oxime and 9-hydroxyrisperidone is not less than 2.8; the tailing factor for risperidone is not less than 1.5; and the relative standard deviation for replicate injections is not less than 2.0% for the risperidone peak.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the responses for the risperidone peak. Calculate the quantity, in percent of $C_{23}H_{27}FN_4O_2$, in the portion of Risperidone taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S and C_U are the concentrations of risperione, in mg per mL, of *Standard preparation* and the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Rubella and Mumps Virus Vaccine Live, *USP 28* page 1743—See briefing under *Diphtheria Toxin for Schick Test*.

(BBVV: T. Morris) RTS—42382-4

Delete the following:

▲~~Rubella and Mumps Virus Vaccine Live~~

~~» Rubella and Mumps Virus Vaccine Live conforms to the regulations of the FDA concerning biologics (see *Biologics* ⟨1041⟩). It is a bacterially sterile preparation of a combination of live rubella virus and live mumps virus such that each component is prepared in conformity with and meets the requirements for Rubella Virus Vaccine Live, and for Mumps Virus Vaccine Live, whichever is applicable. It may contain suitable antimicrobial agents.~~

~~**Packaging and storage**—Preserve in single-dose containers, or in light-resistant, multiple-dose containers, at a temperature between 2° and 8°. Multiple-dose containers for 50 doses are adapted for use only in jet injectors, and those for 10 doses for use by jet or syringe injection.~~

~~**Expiration date**—The expiration date is 1 to 2 years, depending on the manufacturer's data, after date of issue from manufacturer's cold storage (−20°, 1 year).~~

~~**Labeling**—Label the Vaccine in multiple-dose containers to indicate that the contents are intended solely for use by jet injector or for use by either jet or syringe injection, whichever is applicable. Label the Vaccine in single-dose containers, if such containers are not light-resistant, to state that it should be protected from sunlight. Label it also to state that constituted Vaccine should be discarded if not used within 8 hours.~~ ▲*USP30*

BRIEFING

Schick Test Control, *USP 28* page 1756—See briefing under *Diphtheria Toxin for Schick Test*.

(BBVV: T. Morris) RTS—42382-5

Delete the following:

▲~~Schick Test Control~~

~~» Schick Test Control conforms to the regulations of the FDA concerning biologics (see *Biologics* ⟨1041⟩). It is Diphtheria Toxin for Schick Test that has been inactivated by heat for use as control for the Schick Test. It meets the requirements of the specific guinea pig test for detoxification by injection of not less than 2.0 mL into each of at least four guinea pigs. The animals are observed daily for 30 days and during this period show no evidence of diphtheria toxin poisoning (extensive necrosis, paralysis, or specific lethality).~~

~~**Packaging and storage**—Preserve at a temperature between 2° and 8°.~~

~~**Expiration date**—The expiration date is not later than 1 year after date of issue from manufacturer's cold storage (5°, 1 year).~~ ▲*USP30*

BRIEFING

Talc, *USP 28* page 1846, and page 3538 of the *Second Supplement*. In order to align the monograph with the text presented in the *Pharmacopeial Discussion Group,* Stage 6 harmonization draft, it is proposed to omit the use of *Cesium chloride solution* in the preparation of the *Test stock solution* in the test for *Limit of calcium*. This change also affects the test for *Limit of aluminum* and, by cross reference, the test for *Content of magnesium*. It is also proposed to add *Cesium chloride solution* to the test for *Limit of aluminum* where it is used in the preparation of the *Standard aluminum solutions*. In addition, the preparation of the *Standard*

In-Process Revision

iron stock solution in the test for *Limit of iron* is revised to comply with the Stage 6 harmonization draft. A *Packaging and storage* section is also included in this proposal.

(EM1: C. Sheehan) RTS—43212-1

Add the following:

▲**Packaging and storage**—Preserve in well-closed containers. No storage requirements specified.▲*USP30*

Change to read:

Limit of iron—

Test stock solution—Weigh 10.0 g of Talc into a conical flask fitted with a reflux condenser, gradually add 50 mL of 0.5 N hydrochloric acid while stirring, and heat on a water bath for 30 minutes. Allow to cool. Transfer the mixture to a beaker, and allow the undissolved material to settle. Filter the supernatant into a 100-mL volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the residue and the beaker with three 10-mL portions of hot water. Wash the filter with 15 mL of hot water, allow the filtrate to cool, and dilute with water to 100.0 mL.

Test solution—Transfer 2.5 mL of the *Test stock solution* to a 100-mL volumetric flask, add 50.0 mL of 0.5 N hydrochloric acid, and dilute with water to volume.

Standard iron stock solution—~~Transfer 863.4 mg of ferric ammonium sulfate to a 100-mL volumetric flask, dissolve in water, add 10 mL of 2 N sulfuric acid, and dilute with water to volume. Pipet 25 mL of this solution into a 100-mL volumetric flask, add 10 mL of 2 N sulfuric acid, dilute with water to volume, and mix. This solution contains the equivalent of 250 µg of iron per mL.~~

▲Prepare a solution containing 4.840 g of ferric chloride in a 150 g per L solution of hydrochloric acid in water to obtain a concentration equivalent to 250 µg of iron per mL. Prepare immediately before use.▲*USP30*

Standard iron solutions—Into four 100-mL volumetric flasks, each containing 50.0 mL of 0.5 N hydrochloric acid, transfer respectively 2.0, 2.5, 3.0, and 4.0 mL of the *Standard iron stock solution,* and dilute each flask with water to volume.

Procedure—Concomitantly determine the absorbance of the *Test solution* and the *Standard iron solutions* at the iron emission line of 248.3 nm with an atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an iron hollow-cathode lamp and an air–acetylene flame. Make any correction using a deuterium lamp: not more than 0.25% of iron is found.

Change to read:

Limit of calcium—

~~*Cesium chloride solution*—Dissolve 2.53 g of cesium chloride in 100 mL of water, and mix.~~

▲▲*USP30*

Lanthanum chloride solution—To 5.9 g of lanthanum oxide slowly add 10 mL of hydrochloric acid, and heat to boiling. Allow to cool, and dilute with water to 100 mL.

Test stock solution—[Caution—Perchlorates mixed with heavy metals are known to be explosive. Take proper precautions while performing this procedure.] Weigh 500 mg of Talc in a 100-mL polytetrafluoroethylene dish, add 5 mL of hydrochloric acid, 5 mL of lead-free nitric acid, and 5 mL of perchloric acid. Stir gently, then add 35 mL of hydrofluoric acid, and evaporate slowly on a hot plate to moist dryness (until about 0.5 mL remains). To the residue, add 5 mL of hydrochloric acid, cover with a watch glass, heat to boiling, and allow to cool. Rinse the watch glass and the dish with water, and transfer into a 50-mL volumetric flask, ~~containing 5 mL of the *Cesium chloride solution*. Rinse the dish again with water,~~

▲▲*USP30*
and dilute with water to volume.

Test solution—Transfer 5.0 mL of the *Test stock solution* to a 100-mL volumetric flask, add 10.0 mL of hydrochloric acid and 10 mL of *Lanthanum chloride solution,* and dilute with water to volume.

Calcium standard stock solution—Dissolve 3.67 g of calcium chloride dihydrate in diluted hydrochloric acid, and dilute with the same solvent to 1000 mL. Immediately before use, pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 100 µg of calcium per mL.

Standard calcium solutions—Into four identical 100-mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of *Lanthanum chloride solution,* transfer respectively 1.0, 2.0, 3.0, and 4.0 mL of *Calcium standard stock solution,* and dilute each flask with water to volume.

Procedure—Concomitantly determine the absorbance of the *Test solution* and the *Standard calcium solutions* at the calcium emission line of 422.7 nm with an atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a calcium hollow-cathode lamp and a nitrous oxide–acetylene flame: not more than 0.9% of calcium is found.

Change to read:

Limit of aluminum—

~~*Cesium chloride solution* and *Test stock solution*—Proceed as directed in the test for *Limit of calcium.*~~

▲*Cesium chloride solution*—Dissolve 2.53 g of cesium chloride in 100 mL of water, and mix.

Test stock solution—Proceed as directed in the test for *Limit of calcium.* Transfer 5 mL of the *Cesium chloride solution* to the 50-mL volumetric flask, prior to transfer of residue, and dilute with water to volume.▲*USP30*

Test solution—Transfer 5.0 mL of the *Test stock solution* to a 100-mL volumetric flask, add 10 mL of the *Cesium chloride solution* and 10.0 mL of hydrochloric acid, and dilute with water to volume.

Aluminum standard stock solution—Dissolve 8.947 g of aluminum chloride in water, and dilute with water to 1000 mL. Immediately before use, pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of 100 µg of aluminum per mL.

Standard aluminum solutions—Into four identical 100-mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of *Cesium chloride solution,* transfer respectively 5.0, 10.0, 15.0, and 20.0 mL of *Aluminum standard stock solution,* and dilute with water to volume.

Procedure—Concomitantly determine the absorbance of the *Test solution* and the *Standard aluminum solutions* at the aluminum emission line of 309.3 nm with an atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an aluminum hollow-cathode lamp and a nitrous oxide–acetylene flame: not more than 2.0% of aluminum is found.

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 23* page 2941, page 3647 of the *Second Supplement,* and page 1414 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to add *Canola Oil* to the *Solvent* and *Vehicle (Oleaginous)* categories and *Oleyl Oleate* to the *Emollient* and *Emulsifying and/or Solubilizing Agent* categories to complement the proposed new monographs for *Canola Oil* and *Oleyl Oleate,* respectively, which appear elsewhere in this issue of *PF.*

(EM1; EM2) RTS—42982-1; 43026-1

Change to read:

Coating Agent

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
▲Cellaburate▲*NF23*
Cellulose Acetate Phthalate (see Cellacefate)
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■1S (*NF24*)

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
■Hypromellose Acetate Succinate■2S (*NF23*)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
■Maltodextrin■2S (*NF23*)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
■Starch, Pregelatinized Modified■1S (*NF23*)
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Emollient
Alkyl (C12-15) Benzoate

▲Oleyl Oleate▲*NF25*
Hydrogenated Soybean Oil

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Diglycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)

▲Oleyl Oleate▲*NF25*
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate

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Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
■Sorbitan Sesquioleate■2S (*NF23*)
■Sorbitan Trioleate■2S (*NF23*)
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Humectant

■Corn Syrup Solids■1S (*NF24*)

■Erythritol■2S (*NF24*)
Glycerin
Hexylene Glycol

■Maltitol■2S (*NF24*)
Propylene Glycol
Sorbitol
■Sorbitol Sorbitan Solution■2S (*NF23*)

■Tagatose■1S (*NF24*)

Change to read:

Ointment Base
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Diethylene Glycol Monoethyl Ether

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Lanolin
Ointment, Hydrophilic
Ointment, White
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Ointment, Yellow
Polyethylene Glycol ■Monomethyl Ether■2S (*NF23*)
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water
Squalane
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Vegetable Oil, Hydrogenated, Type II

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion
▲Cellaburate▲*NF23*
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■1S (*NF24*)
▲Sodium Tartrate▲*NF23*

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

▲Canola Oil▲*NF25*
■Caprylocaproyl Polyoxylglycerides■1S (*NF23*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

▲Lauroyl Polyoxylglycerides▲*NF24*
■Linoleoyl Polyoxylglycerides■1S (*NF23*)
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
■Oleoyl Polyoxylglycerides■1S (*NF23*)
Peanut Oil
Polyethylene Glycol
■Polyethylene Glycol Monomethyl Ether■2S (*NF23*)
Propylene Glycol
Sesame Oil
■Stearoyl Polyoxylglycerides■1S (*NF23*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
■Alamic Acid■2S (*NF23*)
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 Copolymer

▲Carbomer Homopolymer▲*NF24*
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■1S (*NF24*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
■Maltodextrin■2S (*NF23*)
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
▲Acesulfame Potassium▲*NF23*
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■1S (*NF24*)
Dextrates
Dextrose
Dextrose Excipient

■Erythritol■2S (*NF24*)
Fructose
▲Galactose▲*NF23*

■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder
Acacia
Alginic Acid

■Amino Methacrylate Copolymer■2S (*NF24*)
■Ammonio Methacrylate Copolymer■1S (*NF23*)
Ammonio Methacrylate Copolymer Dispersion

▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
■Copovidone■1S (*NF23*)

■Corn Syrup Solids■1S (*NF24*)
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
■Low-Substituted Hydroxypropyl Cellulose■2S (*NF23*)
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
■Hypromellose Acetate Succinate■2S (*NF23*)
■Maltodextrin■2S (*NF23*)
Maltose
Methylcellulose
Polyethylene Oxide
Povidone
▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Syrup

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■1S (*NF24*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose Monohydrate

■Maltitol■2S (*NF24*)
■Maltodextrin■2S (*NF23*)
Maltose
Mannitol
Sorbitol
■Starch■2S (*NF23*)

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▲Starch, Corn▲*NF23*
▲Starch, Potato▲*NF23*
Starch, Pregelatinized
■Starch, Pregelatinized Modified■1S (*NF23*)
Starch, Tapioca
▲Starch, Wheat▲*NF23*
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

■Corn Syrup Solids■1S (*NF24*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■1S (*NF24*)
■Dextrose■2S (*NF23*)
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil

▲Canola Oil▲*NF25*
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

Canola Oil. Because there is no existing *NF* monograph for this product, it is proposed to add a new monograph based on the Canola Oil monograph in the *Food Chemicals Codex, Fifth Edition,* page 86 and also on the *Cottonseed Oil* monograph in *NF 23,* page 2991.

(EMC: D. Bempong; NL: W. Paul) RTS—43026-1

Add the following:

▲Canola Oil

Low erucic acid rapeseed oil

LEAR oil

» Canola Oil is the refined fixed oil obtained from the seeds of *Brassica napus* or *Brassica campestris* (Fam. Cruciferae). A suitable antioxidant may be added.

Packaging and storage—Preserve in tight containers, and avoid contact with metals. Fill to the top or flush partially filled containers with nitrogen. No storage requirements specified.

Labeling—Label it to indicate the name and concentration of any added antioxidant.

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Identification—It meets the requirements of the test for *Fatty acid composition*.

Specific gravity ⟨841⟩**:** between 0.906 and 0.920.

Acid value ⟨401⟩**:** not more than 6.0.

Iodine value ⟨401⟩**:** between 110 and 126.

Peroxide value ⟨401⟩**:** not more than 10.0.

Saponification value ⟨401⟩**:** between 178 and 193.

Unsaponifiable matter ⟨401⟩**:** not more than 1.5%.

Fatty acid composition—Canola Oil exhibits the following composition profile of fatty acids, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
<14	—	<0.1
14	0	<0.2
16	0	<6.0
16	1	<1.0
18	0	<2.5
18	1	>50
18	2	<40
18	3	<14
20	0	<1.0
20	1	<2.0
22	0	<0.5
22[1]	1	≤2.0
24	0	<0.2
24	1	<0.2

[1] Erucic acid

Refractive index ⟨831⟩**:** between 1.465 and 1.467 at 40°.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Limit of erucic acid: not more than 2.0%, as determined in the test for *Fatty acid composition.*▲*NF25*

BRIEFING

Ethylcellulose Aqueous Dispersion, *NF 23* page 3004 and page 811 of *PF* 31(3) [May–June 2005]. It is proposed to revise the labeling statement to state that the names and quantities of any added antifoaming and antimicrobial agents should be indicated. Editorial changes have been made to *Identification* test *A*.

(EMC: C. Sheehan) RTS—42994-2

Change to read:

Labeling—The labeling states the ethoxy content of the Ethylcellulose and the percentage of Ethylcellulose.

▲The labeling also indicates the names and quantities of any added antifoaming and antimicrobial agents.▲*NF25*

Change to read:

Identification—

A: ~~Transfer a small quantity to a silver chloride plate, and allow the water to evaporate:~~

▲Separately dissolve a small quantity of sample and about 250 mg of USP Ethylcellulose RS in 5 mL of a mixture of toluene and alcohol (80 : 20), transfer a few mL of each solution to a silver chloride plate, and evaporate the solution on each plate:▲*NF25*
the IR absorption spectrum of the residue in the 3600 to 2600 cm^{-1} and 1500 to 800 cm^{-1} regions exhibits maxima only at the same wave numbers as that of a film of USP Ethylcellulose RS prepared ~~as directed in the test for *Identification* under *Ethylcellulose*~~.

▲by dissolving about 250 mg of USP Ethylcellulose RS in 5 mL of a mixture of toluene and alcohol (80 : 20) and evaporating a few mL on a silver chloride plate.▲*NF25*

B: Transfer about 2 mL to a 100-mm diameter petri dish so that the bottom of the dish is covered uniformly. Place the dish in an oven or on a hot plate to evaporate the water: a transparent film results.

C: Dissolve the film formed in *Identification* test *B* in 20 mL of chloroform. Inject 2 µL of this solution into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a 2-mm × 1.8-m column that contains 10% liquid phase G1 on support

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S1A maintained at a temperature of 220° and a flame-ionization detector. The temperatures of the injection port and the detector are maintained at about 250° and 275°, respectively. The retention time of the major peak following the solvent peak in the resulting chromatogram corresponds to that obtained from a similar solution of USP Cetyl Alcohol RS.

D: *Methylene blue solution*—To a 150-mL graduated beaker containing 0.7 mL of sulfuric acid and 5 g of anhydrous sodium sulfate slowly add water to the 90-mL mark. Add methylene blue solution (3 in 1000) to the 100-mL mark, and mix.

Procedure—To 1 mL of Aqueous Dispersion in a 100-mL graduated mixing cylinder add 9 mL of water followed by 25 mL of *Methylene blue solution*, and mix. Add 15 mL of chloroform, and shake vigorously. Allow the two phases to separate: the lower phase is blue, indicating the presence of sodium lauryl sulfate.

BRIEFING

Glyceryl Monostearate, *NF 23* page 3015, page 3357 of the *First Supplement,* and page 495 of *PF* 31(2) [Mar.–Apr. 2005]. On the basis of comments received, it is proposed to add a labeling statement to indicate the name and quantity of any added antioxidant.

(EMC: C. Sheehan) RTS—42994-1

Add the following:

▲**Labeling**—Label it to indicate the name and quantity of any added antioxidant.▲*NF25*

Delete the following:

▲~~**USP Reference standards** ⟨11⟩ *USP Monoglycerides RS.*~~▲*NF24*

Change to read:

Assay for monoglycerides—

~~*Propionating reagent*—Mix 10 mL of pyridine and 20 mL of propionic anhydride.~~

~~*Internal standard solution*—Transfer about 400 mg of hexadecyl hexadecanoate, accurately weighed, to a 100-mL volumetric flask, dissolve in chloroform, dilute with chloroform to volume, and mix.~~

~~*Standard preparation*—Transfer about 50 mg of USP Monoglycerides RS, accurately weighed, to a 25-mL conical flask, add by pipet 5 mL of *Internal standard solution,* and mix. When solution is complete, immerse the flask in a water bath maintained at a temperature between 45° and 50°, and volatilize the chloroform with the aid of a stream of nitrogen. Add 3.0 mL of *Propionating reagent,* and heat on a hot plate at 75° for 30 minutes. Evaporate the reagents with the aid of a stream of nitrogen and gentle steam heat. Add 15 mL of chloroform, and swirl to dissolve the residue.~~

~~*Assay preparation*—Transfer about 50 mg of Glyceryl Monostearate, accurately weighed, to a 25-mL conical flask, and proceed as directed for *Standard preparation,* beginning with "add by pipet 5 mL of *Internal standard solution*."~~

~~*Chromatographic system*—Under typical conditions the instrument is equipped with a flame-ionization detector, and contains a 4-mm × 2.4-m borosilicate glass column packed with 2% liquid phase G27 on 80- to 100-mesh support S1A. The column is maintained isothermally at a temperature between 270° and 280°, the injection port and detector block temperature are maintained at about 310°, and helium is used as the carrier gas at a flow rate of about 70 mL per minute.~~

~~*System suitability*—Chromatograph six to ten injections of the *Standard preparation* as directed for *Procedure:* the resolution factor, *R,* between the peaks for the derivatized glyceryl hexadecanoate and glyceryl octadecanoate is not less than 2.0, and the relative standard deviation of the ratio of the peak area of the derivatized glyceryl octadecanoate to that of the hexadecyl hexadecanoate is not more than 2.0%.~~

~~*Procedure*—Inject a suitable portion of the *Standard preparation* into a suitable gas chromatograph, and record the chromatogram. Measure the areas under the peaks, and record the values of the sum of the areas under the derivatized monoglyceride peaks and of the area under the hexadecyl hexadecanoate peak as A_u and A_s, respectively. Calculate the response factor, F, by the formula:~~

$$~~(A_u/A_s)(W_s/W_u),~~$$

~~in which W_u and W_s are the weights, in mg, of hexadecyl hexadecanoate and USP Monoglycerides RS, respectively, in the *Standard preparation.* Similarly inject a suitable portion of the *Assay preparation,* and record the chromatogram. Measure the areas under the peaks, and record the values of the sum of the areas under the derivatized monoglyceride peaks and of the area under the hexadecyl hexadecanoate peak as a_u and a_s, respectively. Calculate the quantity, in mg, of monoglycerides in the amount of Glyceryl Monostearate taken by the formula:~~

$$~~(W_s/F)(a_u/a_s),~~$$

~~in which the terms are as defined therein.~~

▲*Mobile phase*—Use tetrahydrofuran.

Assay preparation—Transfer about 40 mg of Glyceryl Monostearate, 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 7.5-mm × 60-cm column containing 5-µm 100-Å packing L21. The column and the detector temperatures are maintained at 40°. [NOTE—Two or three 7.5-mm × 30-cm L21 columns may be used in place of the one 60-cm column, provided that system suitability requirements are met; and the column temperature may be lowered to ambient temperature, although working at 40° provides stable separation conditions and ensures better sample solu-

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bility.] The flow rate is about 1 mL per minute. 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 relative standard deviation for replicate injections determined from the monoglycerides peak is not more than 2.0%.

Procedure—Inject a volume (about 40 µL) of the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of monoglycerides in the portion of Glyceryl Monostearate taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for the monoglycerides; and r_s is the sum of the responses for all the glyceride peaks.▲*NF24*

BRIEFING

Oleyl Oleate. Because there is no existing *NF* monograph for this excipient, a new monograph is being proposed, based on the *Oleyl Oleate* monograph in the *Japanese Pharmaceutical Excipients Directory 1996,* page 346, and the *Ethyl Oleate* monograph in *USP 28–NF 23,* page 3003.

(EMC: D. Bempong) RTS—42982-1

Add the following:

▲Oleyl Oleate

$C_{36}H_{68}O_2$ 532.94

9-Octadecenoic acid, *(Z)-,* oleyl ester.

Oleyl oleate [*3687-45-4*].

» Oleyl Oleate consists of esters of oleyl alcohol and high molecular weight fatty acids, principally oleic acid.

Packaging and storage—Preserve in tight containers. No storage conditions specified.

USP Reference standards ⟨11⟩—*USP Oleyl Oleate RS.*

Clarity of solution—Dissolve 2.0 g in 10 mL of ether: the resulting solution is clear.

Identification, *Infrared Absorption* ⟨197F⟩.

Specific gravity ⟨841⟩**:** between 0.860 and 0.884 at 20°.

Acid value ⟨401⟩**:** not more than 3.0.

Hydroxyl value ⟨401⟩**:** not more than 10.

Iodine value ⟨401⟩**:** between 70 and 120.

Saponification value ⟨401⟩**:** between 90 and 125.

Refractive index ⟨831⟩**:** between 1.464 and 1.468 at 20°.

Residue on ignition ⟨281⟩**:** not more than 0.1%, a 2-g specimen being used.

Arsenic, *Method II* ⟨211⟩**:** 2 µg per g.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.▲*NF25*

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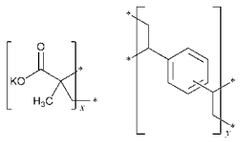
BRIEFING

Polacrilin Potassium, *NF 23* page 3050. It is proposed to correct the CAS number and to revise the chemical name of the material.

(EM2: H. Wang) RTS—43173-1

Change to read:



~~2-Propenoic acid, 2-methyl-, polymer with divinylbenzene, potassium salt.~~

▲2-Propenoic acid, 2-methyl-, potassium salt, polymer with diethenylbenzene.▲*NF25*

~~Methacrylic acid polymer with divinylbenzene, potassium salt~~

▲Potassium methacrylate-divinylbenzene copolymer▲*NF25* [~~*39394-76-5*~~

▲*65405-55-2*].▲*NF25*

BRIEFING

Polyoxyl 35 Caster Oil, *NF 23* page 3060 and page 3656 of the *Second Supplement*. On the basis of comments received, it is proposed to revise the lower limit in the test for *Viscosity* from 650 centipoises to 600 centipoises.

(EM2: H. Wang) RTS—43001-2

Change to read:

Viscosity ⟨911⟩: between ~~650~~

▲600▲*NF25*
and 850 centipoises at 25°, a capillary viscosimeter being used.

BRIEFING

Sorbitol Sorbitan Solution, page 3656 of the *Second Supplement*. It is proposed to revise the statement appearing directly below the Title to provide further clarification on Title change and labeling of this excipient. In the absence of any adverse comments, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2006.

(EM1: C. Sheehan; NOM: W. Paul) RTS—43172-1

Sorbitol Sorbitan Solution

Change to read:

(Title for this monograph—to become official August 1, 2010)
~~(Prior to August 1, 2010, it is expected that the current practice of labeling the article of commerce with the name Anhydrized Liquid Sorbitol will be continued.)~~

•***(Prior to August 1, 2010, the current practice of labeling the article of commerce with the name Anhydrized Liquid Sorbitol may be continued. Use of the name Sorbitol Sorbitan Solution will be permitted as of August 1, 2005, but the use of this name will not be mandatory until August 1, 2010. The 60-month extension will provide the time needed by the manufacturers and users to make necessary changes.)***•2

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BRIEFING

Tetrafluoroethane. Because there is no existing *NF* monograph for this excipient, a new monograph, based on submitted data, is being proposed. In *Chromatographic purity Test 1* and *Test 2,* the typical retention times for tetrafluoroethane are about 13 minutes and 9 minutes, respectively; for a description of the phases and supports for the columns used in *Test 1,* please see *Chromatographic Reagents* under the general chapter *Chromatography* ⟨621⟩, which appears elsewhere in this issue.

(AER: K. Zaidi) RTS—34836-2

Add the following:

▲Tetrafluoroethane

$C_2H_2F_4$ 102.03

1,1,1,2-Tetrafluoroethane [*811-97-2*].

»Tetrafluoroethane contains not less than 99.9 percent and not more than 100.0 percent of $C_2H_2F_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in contamination-free tight containers, reserved for pharmaceutical propellants, and specifically designed for transport and storage of liquefied refrigerant gases. Protect from excessive heat.

USP Reference standards ⟨11⟩**—***USP Tetrafluoroethane RS. USP Tetrafluoroethane Related Compound Mixture 1 RS. USP Tetrafluoroethane Related Compound Mixture 2 RS.*

Identification—The IR absorption spectrum of 1,1,1,2-tetrafluoroethane determined in a 10-cm gas cell with sodium chloride windows, at atmospheric pressure, exhibits maxima, among others, at the following wavelengths, in µm: 3.4(m), 4.4(m), 7.0(m), 7.7(vs), 8.4(vs), 9.1(s), 10.3(s), 11.9(m), and 15.0(s). The stronger maxima are best obtained at pressures less than 19 mm of mercury.

Water—Determine the water content by using an instrument designed specifically for measuring moisture in refrigerants.* Follow the instrument manufacturer's instructions, and connect the instrument directly to the bulk propellant container. Enter the molecular weight of the gas (102 Da for 1,1,1,2-tetrafluoroethane) to convert volumetric flow rate to mass flow rate. Set the vapor flow rate to 1100 cc per minute. When a stable reading on the digital display is achieved (about 15 minutes), record the mass of water present, in ppm. Not more than 10 ppm is found.

High-boiling residues—Proceed as directed for *General Sampling Procedure* in *Propellants* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ to collect a sample of propellant. *[Caution—Contact with liquid propellant can cause severe frostbite.]* Attach a clean Teflon tube (20-cm length × about 6-mm OD) to the cylinder valve. Weigh the cylinder (with tubing) to the nearest 0.1 g. Prepare a vessel in which the propellant can be collected and then evaporated in a fume hood and weighed with precision and accuracy. Typically, an empty, clean, dry aluminum beverage can from which the top has been removed is suitable. [NOTE—The top may easily be removed by trimming 1 or 2 mm off the bead around the top of the beverage can with tin snips.] Handle the vessel with clean,

* An instrument such as the IceMan, manufactured by MEECO, Inc., Warrington, PA, is suitable.

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dry cotton gloves or appropriate tongs. Tare the vessel to the nearest 0.0001 g. Set the vessel on a clean paper towel in a fume hood. With the sample cylinder inverted to deliver liquid propellant from the attached tube, open the valve carefully to discharge propellant into the vessel tangentially, to cause swirling of the fluid against the vessel wall, until the vessel is about half full. [NOTE—Cooling created by the propellant gas impinging on the wall of the vesssel will liquefy the gas.] Dry any condensed water off the sample cylinder tube, and set the cylinder aside with the tube still attached. Allow the propellant to evaporate from the sample vessel. After the propellant has evaporated, dry the outside of the vessel by gently wiping the condensed moisture from the outside of the vessel with a lint-free towel. Place the vessel on a hot plate, and set to 80 ± 5° (monitored with a surface thermometer) for 5 minutes. Allow the vessel to cool to room temperature. Weigh the vessel to the nearest 0.0001 g, and weigh the sample cylinder to the nearest 0.1 g. From the sample size (weight lost from the sample cylinder and tubing) and the weight gained by the vessel, calculate the concentration, in percentage, of high-boiling residue in the propellant by the formula:

$$\text{Percentage residue} = 100(W_R / W_S)$$

in which W_R is the weight of residue, and W_S is the weight of the propellant sample: not more than 0.01% (w/w) is found.

Ionic contaminants—[NOTE—Use a suitable conductivity meter equipped with a dip cell that has a cell constant of 0.1 cm^{-1}. Convert all conductivity measurements to specific conductivity by multiplying the meter reading by the cell constant. Record the specific conductivity.]

Conductivity, C_1, of the deionized water—Proceed as directed for *General Sampling Procedure* in *Propellants* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ to collect at least 100 g of propellant (100 to 120 g). Attach a clean, dry heavy-walled Teflon tubing (25-cm length × 3-mm OD) to the valve of the sample cylinder. Weigh the cylinder tubing assembly to the nearest 0.5 g, and record the weight as S_1. Reserve a 250-mL narrow-mouth polyethylene bottle with a polyethylene screw cap for this test. Calibrate this bottle with 100 mL of water (mark the level on the outside of the bottle). Copiously rinse the bottle and cap with deionized water having a specific conductivity not greater than 0.5 microSiemens (μS). Discard the water, then air-dry the bottle and cap. Weigh the bottle and cap to the nearest 0.5 g, and record as the tare weight, W_1. Fill the bottle to the 100-mL mark with deionized water (specific conductivity not greater than 0.5 μS), and cap. Weigh and record the weight of the bottle containing the water to the nearest 0.5 g, W_2. Vigorously shake the bottle for about 20 seconds to equilibrate the water with any carbon dioxide present in the headspace air in the bottle. Clamp the bottle in a 25° water bath; the water level in the bottle should be slightly below that of the water in the bath to allow the water in the bottle to equilibrate to 25 ± 0.5°. Carefully measure the conductivity, in μS, of the water in the polyethylene bottle. Record this conductivity as C_1.

Conductivity, C_2, of the aqueous extractant—Position the cylinder containing the sample on a ring stand so that liquid sample can be discharged through the Teflon tubing into the deionized water extractant. The discharge end of the tubing should be positioned in the extractant to within about 6 mm

from the bottom of the polyethylene bottle. Open the valve on the sample cylinder slowly, to allow the sample to bubble through the water (extractant) at a moderate rate. (It will require approximately 40 to 50 minutes to deliver 80 to 100 g of sample.) When the required sample has been delivered, close the valve on the sample cylinder; then, raise the sample cylinder so that the end of the Teflon tubing is clear of the polyethylene bottle. Cap the bottle. Allow the water in the bottle to re-equilibrate to 25 ± 0.5°. Carefully remove the cap of the bottle (some propellant gas may escape as a result of temperature change), and measure the conductivity of the aqueous extractant. Record this specific conductivity, in µS, as C_2.

Total ionic contamination—Wipe dry the Teflon tubing; then, weigh the sample cylinder with the tubing to the nearest 0.5 g. Record this weight as sample weight S_2. Calculate the total ionic contamination, as HCl, in parts per billion (ppb) by weight, by the following formula:

$$HCl_{ppb} = 85.5CE/0.997P$$

in which 85.5 is the factor used to convert specific conductivity, in µS, to nanograms of HCl; C is the change in specific conductivity, in µS, due to acidity extracted from the propellant that is collected in the aqueous extract ($C_2 - C_1$); E is the weight in g, of the aqueous extract ($W_2 - W_1$); 0.997 is the density of water, in g per cm³, at 25°; and P is the propellant sample weight ($S_1 - S_2$). Total acidity as HCl, as determined above, must not exceed 100 ppb. [NOTE—The factor used above for converting specific conductivity to weight of HCl in the extractant, 85.5 nanograms of HCl per µS, is based on standard formulas, using the literature standard value for equivalent conductivity of HCl, at near infinite dilution at 25°, of 426 Siemens cm²/equivalent. Conductivity measurements are made at 25° to avoid temperature compensation problems often present in conductivity meters.]

Chromatographic purity—

TEST 1—

Standard solution—Use USP Tetrafluoroethane Related Compound Mixture 1 RS.

Test solution—Proceed as directed for *General Sampling Procedure* in *Propellants* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ to collect a sample of tetrafluoroethane from the bulk container.

Chromatographic system (see *Chromatography* ⟨621⟩)—Connect the four packed columns in series, in the order listed in *Table 1*.

Table 1*

Phase	Support	Length
G##	100/120 mesh S1A	6 ft (nominal 1.83 m)
G##	60/80 mesh S12	6 m
G25 or G35	60/80 mesh S12	16 ft (nominal 4.88 m)
	S##	1 ft (nominal 30.5 cm)

* The 1/8-inch (nominal 3.2-mm) OD stainless steel packed columns must be connected in series in the order listed.

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Column 1 must be connected directly to the injection port. The chromatograph settings are shown in *Table 2.*

Table 2. Chromatograph Settings for *Test 1* (Packed Column)*

Columns: four packed columns (listed in *Table 1*) connected in series, with column 1 connected directly to the injection port
Maximum safe column temperature: 180°
Column compensation: none
Injection port: liquid valve; sample size: 0.2 µL
Injector temperature: 200°
Detector: flame ionization; gas settings: hydrogen—30 mL per minute, air—300 mL per minute
Detector temperature: 200°
Carrier gas: helium at 20 mL per minute
Programming:
Initial column temperature: 40°
Initial hold: 6 minutes
Temperature rise: 10° per minute
Final temperature: 165°; hold: 26.0 minutes
Total run time: 45 minutes

* Possible impurities detected are listed in *Table 3.*

Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the retention time for tetrafluoroethane is about 13 minutes.

Procedure—Pressurize the cylinders containing the *Standard solution* and the *Test solution* to 150 ± 10 PSIG (1 mPa ± 70 kPa gauge) with nitrogen. Invert the cylinders to ensure liquid delivery. Attach the inverted cylinders to the injection valve of the chromatograph with a short but convenient length of 3-mm OD translucent Teflon tubing. Open the cylinder valve. Flush the tubing and the injection valve by intermittently opening and closing the exit valve, which is attached to the exit side of the injection valve with a short piece of tubing, to ensure that the injection valve is full of liquid and bubble free. Separately inject about 0.2 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 ppm of each impurity in the sample of Tetrafluoroethane taken by the formula:

$$C = C_S r_i / r_S$$

in which C is the concentration, in ppm, of impurities in the *Test solution;* C_S is the concentration, in ppm, of impurities in the *Standard solution;* r_i is the peak area of each impurity obtained from the *Test solution;* and r_S is the peak area of each impurity obtained from the *Standard solution.* In addition to not exceeding the limits for each impurity shown in *Table 3* and *Table 5*, not more than 5 ppm of other identified saturated impurities are found; not more than 5 ppm of any individual unidentified impurity is found; and not more than 10 ppm of total unidentified impurities is found.

Table 3. Impurities Listing for Packed Column *(Test 1)*

Impurity Number	Chemical Name	Maximum Allowed (ppm)	Retention Time Relative to HFC-134a
HFC-1123[c] (unsaturated halocarbon)	1,2,2-Trifluoroethene	5[a]	0.881
HFC-143a[c] (saturated hydrofluorocarbon)	2,2,2-Trifluoroethane	20	0.916
HFC-161[c] (saturated hydrofluorocarbon)	Fluoroethane	30	0.976[b]
HFC-125 (saturated hydrofluorocarbon)	1,1,2,2,2-Pentafluoroethane	5	0.976 [b]
HFC-134a[c] (saturated hydrofluorocarbon)	1,1,1,2-Tetrafluoroethane	—	1
CFC-115[c] (saturated chlorofluorocarbon)	1-Chloro-1,1,2,2,2-pentafluoroethane	5	1.260
HFC-1243zf[c] (unsaturated halocarbon)	1,1,1-Trifluoropropene	5[a]	1.303[b]
HFC-1132 (unsaturated halocarbon)	1,2-Difluoroethene	5[a]	1.303[b]
HFC-245cb (saturated hydrofluorocarbon)	1,1,1,2,2-Pentafluoropropane	5	1.303[b]
HFC-1234yf[c] (unsaturated halocarbon)	1,1,1,2-Tetrafluoropropene	5[a]	1.317
CFC-12[c] (saturated chlorofluorocarbon)	Dichlorodifluoromethane	100	1.37
HFC-1225ye[c] (unsaturated halocarbon)	1,2,3,3,3-Pentafluoropropene	5[a]	1.423
HCFC-1122[c] (unsaturated halocarbon)	2-Chloro-1,1-difluoroethene	5[a]	1.451
HCFC-124[c] (saturated hydrochlorofluorocarbon)	1-Chloro-1,2,2,2-tetrafluoroethane	100	1.479
HCFC-133a[c] (saturated hydrochlorofluorocarbon)	1-Chloro-2,2,2-trifluoroethane	5	1.534

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Table 3. Impurities Listing for Packed Column *(Test 1)* *(Continued)*

Impurity Number	Chemical Name	Maximum Allowed (ppm)	Retention Time Relative to HFC-134a
FC-1318my-Trans[c] (unsaturated halocarbon)	Octafluorobutene	5[a]	1.687
CFC-114[c] (saturated chlorofluorocarbon)	1,2-Dichloro-1,1,2,2-tetrafluoroethane	5	1.807
CFC-114a[c] (saturated chlorofluorocarbon)	1,1-Dichloro-1,2,2,2-tetrafluoroethane	25	1.83
CFC-11[c] (saturated chlorofluorocarbon)	Trichlorofluoromethane	5	2.054
CFC 1112a[c] (unsaturated halocarbon)	1,1-Dichloro-2,2-difluoroethene	5[a]	2.140
HCFC-123[c] (saturated hydrochlorofluorocarbon)	1,1-Dichloro-2,2,2-trifluoroethane	5	2.251
HCFC-1121[c] (unsaturated halocarbon)	1,2-Dichloro-2-fluoroethene	5[a]	2.333
CFC-113 (saturated chlorofluorocarbon)	1,1,2-Trichloro-1,2,2-trifluoroethane	5	2.767

[a] The maximum allowable concentration of the unsaturated compounds listed here, along with those determined with the capillary column method (*Test 2*) described below, in aggregate, must not exceed 5 ppm by weight of tetrafluoroethane.
[b] HFC-125 and HFC-161 coelute. Determine composition by gas chromatography/mass spectroscopy. HFC-1243zf, HFC-1132, and HFC-245cb coelute. Determine composition by gas chromatography/mass spectroscopy.
[c] These impurities are present in USP Tetrafluoroethane Related Compound Mixture 1 RS.

TEST 2—

Standard solution—Use USP Tetrafluoroethane Related Compound Mixture 2 RS.

Test solution—Proceed as directed for the *General Sampling Procedure* in *Propellants* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ to collect a sample of Tetrafluoroethane from the bulk container.

Chromatographic system (see *Chromatography* ⟨621⟩—See *Table 4* for the chromatographic system settings.

Table 4. Chromatograph Settings for *Test 2* (Capillary Column Method)*

Columns: Supelco fused silica capillary, 0.25 mm × 60 m, 1-µm film substrate, DB-1301 (USP G43)
Maximum safe column temperature: 250°
Column compensation: nitrogen makeup gas, 18 mL per minute
Injection port and sample size: gas valve, 0.5 µL, split ratio 150 : 1
Injector temperature: 200°
Detector: flame ionization; gas settings: hydrogen—30 mL per minute, air—300 mL per minute
Detector temperature: 250°
Carrier gas: helium at 0.7 mL per minute
Programming:
Initial column temperature: –20°
Initial hold: 12 minutes
Temperature rise: 10° per minute
Final temperature: 50°; hold: 5.00 minutes
Total run time: 24 minutes

* Possible impurities detected are listed in *Table 5.*

Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the retention time for tetrafluoroethane is about 9 minutes.

Procedure—Attach the cylinder containing the USP Tetrafluoroethane Related Compound Mixture 2 RS upright to the injection valve of the chromatograph by means of a short but convenient length of 3-mm OD translucent Teflon tubing. The cylinder must be held upright to ensure vapor delivery. Open the cylinder valve. Flush the tubing and the injection valve by intermittently opening and closing the exit valve, which is attached to the exit side of the injection valve by means of a short piece of tubing, to ensure that the injection valve is bubble free. Separately inject about 0.5 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 ppm of each impurity in the sample of Tetrafluoroethane taken by the formula:

$$C = C_S r_i / r_S$$

in which C is the concentration, in ppm, of impurities in the *Test solution;* C_S is the concentration, in ppm, of impurities in the *Standard solution;* r_i is the peak area of each impurity obtained from the *Test solution;* and r_S is the peak area of each impurity obtained from the *Standard solution.* In addition to not exceeding the limits for each impurity shown in *Table 3* and *Table 5*, not more than 5 ppm of other identified saturated impurities is found; not more than 5 ppm of any individual unidentified impurity is found; and not more than 10 ppm of total unidentified impurities is found.

Table 5. Impurities Listing for Capillary Column Method (*Test 2*)

Impurity Number	Chemical Name	Maximum Allowed (ppm)	Retention Time Relative to HFC-134a
HFC-1225zc[a] (unsaturated halocarbon)	1,1,1,3,3-Pentafluoropropene	[b]	0.987
HFC-134a[a] (saturated hydrofluorocarbon	1,1,1,2-Tetrafluoroethane	—	1.000
HFC-152a[a] (saturated hydrofluorocarbon)	1,1-Difluoroethane	300	1.110
HFC-134[a] (saturated hydrofluorocarbon)	1,1,2,2-Tetrafluoroethane	1000	1.183
HCFC-22[a] (saturated hydrochlorofluorocarbon)	Chlorodifluoromethane	50	1.288
HCC-40[a] (saturated chlorocarbon)	Chloromethane	5	1.578
HCC-1140[a] (unsaturated chlorocarbon)	1-Chloroethene (vinyl chloride)	[b]	1.793
HCFC-31[a] (saturated hydrochlorofluorocarbon)	Chlorofluoromethane	5	1.809

[a] These impurities are present in USP Tetrafluoroethane Related Compound Mixture 2 RS.
[b] The maximum allowable concentration of the unsaturated compounds listed here, along with those determined with the packed column method described above, in aggregate, must not exceed 5 ppm by weight of Tetrafluoroethane.

Assay—Using the results of the tests for *High-boiling residues* and *Chromatographic purity,* calculate the percentage of tetrafluoroethane ($C_2H_2F_4$) in the sample of Tetrafluoroethane taken by subtracting from 100.0% the total percentages of all the impurities found.▲*NF25*

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 28* page 2204, page 3557 of the *Second Supplement,* the *Third Interim Revision Announcement* on page 710 of *PF* 31(3) [May–June 2005], the *Fourth Interim Revision Announcement* on page 1017 of *PF* 31(4) [July–Aug. 2005], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], and page 1433 of *PF* 31(5) [Sept.–Oct. 2005].

(HDQ) RTS—34836-2; 39955-1; 42021-1; 42740-1; 42823-1; 42982-1; 43014-1; 43125-1; 43126-2; 43127-1; 43292-1

Add the following:

▲USP Amitriptyline Related Compound A RS—[To come.]▲*USP30*

Add the following:

▲USP Amitriptyline Related Compound B RS—[To come.]▲*USP30*

Add the following:

▲USP Calcium Lactate RS—[To come.]▲*USP30*

Change to read:

USP Clonidine Related Compound B RS [2-[(*E*)-2,6-dichlorophenylimino]-1-(1-{2-[(*E*)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)-imidazolidine] ~~($C_{24}H_{24}Cl_4N_6$ ✧ 485.24)~~

▲($C_{20}H_{20}Cl_4N_6$ ✧ 486.23)▲*USP30*

—Do not dry. Keep container tightly closed. Protect from light.

Add the following:

▲USP Cytosine RS—[To come.]▲*USP30*

Add the following:

▲USP Estradiol Related Compound A RS [α-estradiol**]**—[To come.]▲*USP30*

Add the following:

▲USP Estradiol Related Compound B RS [6-dehydro-estradiol**]**—[To come.]▲*USP30*

Delete the following:

~~▲■USP Fluvastatin Related Compound A RS [fluvastatin hydroxydione].■*1S (USP28)*▲*USP30*~~

Change to read:

USP

•Diluted•[2]
Isosorbide Mononitrate RS.

Add the following:

▲USP Levocabastine Hydrochloride RS—[To come.]▲*USP30*

Add the following:

▲USP Levocabastine Related Compound A RS—[To come.]▲*USP30*

Add the following:

▲USP Oleyl Oleate RS—[To come.]▲*USP30*

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Add the following:

▲**USP Risperidone RS** [3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one] (410.48 ✧ CAS-106266-06-2)—Do not dry before using. Keep container tightly closed.▲*USP30*

Add the following:

▲**USP Risperidone System Suitability Mixture RS**—Do not dry before using. Keep container tightly closed. Contains risperidone and about 0.2% of each of the following:

Z-oxime-3-[2-[4-[(*Z*)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

9-hydroxyrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

6-methylrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.▲*USP30*

Add the following:

▲**USP Tetrafluoroethane RS**—[To come.]▲*USP30*

Add the following:

▲**USP Tetrafluoroethane Related Compound Mixture 1 RS**—[To come.]▲*USP30*

Add the following:

▲**USP Tetrafluoroethane Related Compound Mixture 2 RS**—[To come.]▲*USP30*

Physical Tests and Determinations

BRIEFING

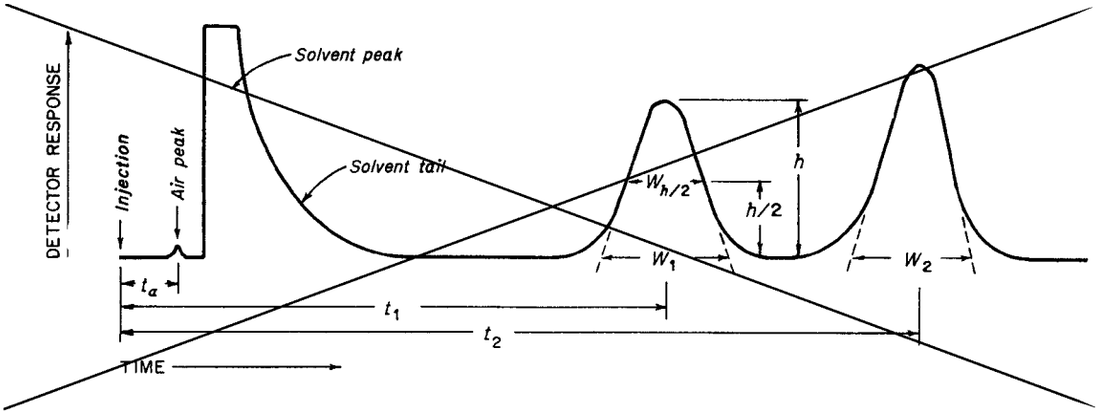
⟨**621**⟩ **Chromatography,** *USP 28* page 2380, page 3566 of the *Second Supplement,* and page 825 of *PF* 31(3) [May–June 2005]. In the *Chromatographic Reagents* section it is proposed to expand the particle size ranges for the designations L1, L7, and L11. Also, some new column designations are being added.

(BPC: M. Marques) RTS—43214-1

Change to read:

INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2, where t_1 and t_2 are the respective retention times; and h, $h/2$, and $W_{h/2}$ are the height, the half-height, and the width at half-height, respectively, for peak 1. W_1 and W_2 are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.



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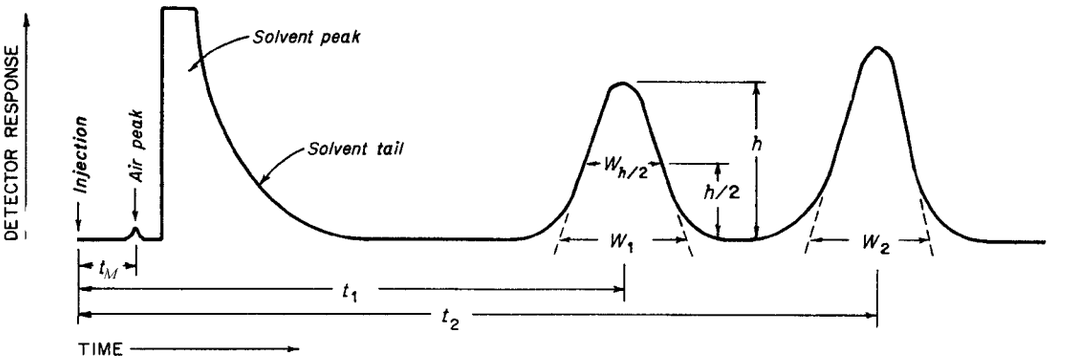

Fig. 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next. ~~Comparisons are normally made in terms of relative retention, α,~~

~~r,~~
~~which is calculated by the equation:~~

$$\alpha = \frac{t_2 - t_a}{t_1 - t_a},$$

$$r = \frac{t_2 - t_a}{t_1 - t_a}$$

~~where t_2 and t_1 are the retention times, measured from the point of injection, of the test and reference substances, respectively, determined under identical experimental conditions on the same column, and t_a is the retention time of a nonretained substance, such as methane in the case of gas chromatography.~~

~~In this and the following expressions, the corresponding retention volumes or linear separations on the chromatogram, both of which are directly proportional to retention time, may be substituted in the equations. Where the value of t_a is small, R_r may be estimated from the retention times measured from the point of injection (t_2/t_1).~~

~~R_r:~~

■Because in most procedures there is no need to identify an unretained peak, comparisons are normally made in terms of relative retention times, R_r:

$$R_r = \frac{t_2}{t_1}$$

where t_2 and t_1 are the retention times, measured from the point of injection, of the test and the reference substances, respectively, determined under identical experimental conditions on the same column.

Other procedures may identify the peak position using the relative retention, r:

$$r = \frac{t_2 - t_M}{t_1 - t_M}$$

where t_M is the retention time of a non-retained marker, which needs to be defined in the procedure.■1S (*USP29*)

The number of theoretical plates, N, is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:

$$N = 16\left(\frac{t}{W}\right)^2 \text{ or } N = 5.54\left(\frac{t}{W_{h/2}}\right)^2,$$

■$N = 16\left(\frac{t}{W}\right)^2$ ■1S (*USP29*)

where t is the retention time of the substance and W is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. ~~$W_{h/2}$ is the peak width at half-height, obtained directly by electronic integrators.~~

■■1S (*USP29*)

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The value of N depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, R, is determined by the equation:

$$R = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

in which t_2 and t_1 are the retention times of the two components, and W_2 and W_1 are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, R, by the equation:

$$R = \frac{2(t_2 - t_1)}{1.70(W_{1,h/2} + W_{2,h/2})}$$

and to determine the number of theoretical plates, N, by the equation:

$$N = 5.54(t/W_{h/2})^2$$

■where $W_{h/2}$ is the peak width at half-height, obtained directly by electronic integrators.■1S *(USP29)*
However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, 0.5% impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

Change to read:

SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the

▲detection sensitivity,▲*USP29*
(Official June 1, 2006)

resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The 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.

▲The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the *Chromatographic purity* or *Related compounds* tests by injecting a volume of a quantitation limit solution equal to that of the *Test solution*. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the *Test solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test solution* in the case of drug substances, and at a 0.1% level relative to the amount of drug substance in the *Test solution* for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.▲*USP29*
(Official June 1, 2006)

The resolution, R, [NOTE—All terms and symbols are defined in the *Glossary of Symbols*] is a function of the column efficiency, N, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, S_R, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.

The tailing factor, *T,* a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see *Figure 2*). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.

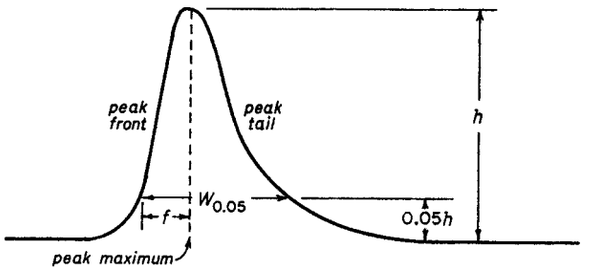

Fig. 2. Asymmetrical chromatographic peak

These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see *Procedures* under *Tests and Assays* in the *General Notices*). ~~Adjustments of operating conditions to meet system suitability requirements may be necessary.~~

■If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum ~~specification~~ variation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when ~~Reference Standards~~ suitable standards (including Reference Standards) are available for all ~~analytes~~ compounds used in the suitability test and only when those standards are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. ~~The changes described below may require additional validation data unless the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.~~ The changes described below may require additional validation data. The user should verify the suitability of the method under the new conditions by assessing the relevant analytical performance characteristics potentially affected by the change. *Tables 1* and *2* in the general information chapter *Verification of Compendial Procedures* ⟨1226⟩ provide lists of analytical performance validation characteristics that may require assessment. Multiple adjustments can have a cumulative effect in the performance of the system and should be considered carefully before implementation.

pH of Mobile Phase (HPLC)—The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within ~~0.2~~ ± 0.2 units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within ± 10%, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC)—~~The amount of the minor~~ The following adjustment limits apply to minor components of the mobile phase (specified at 50% or less). The amount(s) of these component(s) can be adjusted by ± 30% relative. ~~or ± 2% absolute (i.e., in relation to the total mobile phase), whichever is larger.~~ However, the change in any component cannot exceed ± 10% absolute (i.e., in relation to the total mobile phase), nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

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Binary Mixtures—

SPECIFIED RATIO OF 50 : 50—Thirty percent of 50 is 15% absolute, but this exceeds the maximum permitted change of ±10% absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40 : 60 to 60 : 40.

~~SPECIFIED RATIO OF 95 : 5 Thirty percent of 5 is 1.5% absolute. However, because adjustments up to ±2% absolute are allowed, the ratio may be adjusted within the range of 93 : 7 to 97 : 3.~~

SPECIFIED RATIO OF 2 : 98—Thirty percent of 2 is 0.6% absolute. ~~In this case an absolute adjustment of ±2% is not allowed because it would reduce the amount of the first component to zero.~~ Therefore the maximum allowed adjustment is within the range of 1.4 : 98.6 to 2.6 : 97.4.

Ternary Mixtures—

SPECIFIED RATIO OF 60 : 35 : 5—For the second component, 30% of 35 is 10.5% absolute, which exceeds the maximum permitted change of ±10% absolute in any component. Therefore the second component may be adjusted only within the range of 25% to 45% absolute. For the third component, 30% of 5 is 1.5% absolute. ~~Since ±2% absolute is permitted and provides more flexibility, the third component may be adjusted within the range of 3% to 7% absolute.~~ In all cases, a sufficient quantity of the first component is used to give a total of 100%. Therefore, mixture ranges of 50 : 45 : 5 to 70 : 25 : 5 or ~~58 : 35 : 7 to 62 : 35 : 3~~ 58.5 : 35 : 6.5 to 61.5 : 35 : 3.5 would meet the requirement.

~~Detector~~ Wavelength of UV-Visible Detector (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, ±3 nm.

Column Length (GC, HPLC): can be adjusted by as much as ~~70%.~~ ±70%.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as ~~±25% 50%.~~ ±25% for HPLC and ±50% for GC.

Film Thickness (Capillary GC): can be adjusted by as much as –50% to 100%.

Particle Size (HPLC): can be reduced by as much as 50%.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as ±50%.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. ~~It may be increased to as much as twice the volume specified, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity, and retention times.~~

Column Temperature (HPLC): can be adjusted by as much as ~~±20°.~~ ±10°. Column thermostating is recommended to improve control and reproducibility of retention time.

~~Column~~ Oven Temperature (GC): can be adjusted by as much as ~~±2%, in terms of absolute temperature.~~ ±10%.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to ±20% is permitted.

~~**Gradient Elution (HPLC)**—The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column.~~ ■1S (*USP29*)

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

■Relative retention times may be provided in monographs for informational purposes only, to aid in peak identification. There are no acceptance criteria applied to relative retention times.■1S (*USP29*)

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.

The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails

■system suitability■1S (*USP29*) requirements are unacceptable.

Change to read:

GLOSSARY OF SYMBOLS

To promote uniformity of interpretation, the following symbols and definitions are employed where applicable in presenting formulas in the individual monographs.

■Where a different symbol or definition is used in an individual monograph, the monograph text takes precedence (see *General Notices*).■1S (*USP29*)

[NOTE—Where the terms W and t both appear in the same equation they must be expressed in the same units.]

~~α relative retention,~~

$$\alpha = \frac{t_2 - t_a}{t_1 - t_a}.$$

~~c_s, c_t, c_u concentrations of Reference Standard, internal standard, and analyte in a particular solution.~~

~~C_u concentration ratio of analyte and internal standard in test solution or *Assay preparation*,~~

$$C_A = \frac{C_u}{C_t}.$$

~~C_s concentration ratio of Reference Standard and internal standard in Standard solution,~~

$$C_S = \frac{C_t}{C_t}.$$

■■1S (*USP29*)

f distance from the peak maximum to the leading edge of the peak, the distance being measured at a point 5% of the peak height from the baseline.

k' capacity factor,

$$k' = \frac{\text{amount of substance in stationary phase}}{\text{amount of substance in mobile phase}}$$

$$k' = \frac{\text{time spent by substance in stationary phase}}{\text{time spent by substance in mobile phase}} = \frac{t}{t_u} - 1.$$

■$$k' = \frac{\text{time spent by substance in stationary phase}}{\text{time spent by substance in mobile phase}} = \frac{t}{t_{ur}} - 1$$■1S (*USP29*)

N number of theoretical plates in a chromatographic column,

$$N = 16\left(\frac{t}{W}\right)^2.$$

■$$N = 16\left(\frac{t}{W}\right)^2 \text{ or } N = 5.54\left(\frac{t}{W_{h/2}}\right)^2$$■1S (*USP29*)

~~q_s, q_t, q_u total quantities (weights) of Reference Standard, internal standard, and analyte in a particular solution.~~

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~~Q_A~~ ~~quantity ratio of analyte and internal standard in test solution or *Assay preparation*,~~

~~$Q_A = \frac{q_u}{q_i}$.~~

~~Q_S~~ ~~quantity ratio of Reference Standard and internal standard in Standard solution,~~

~~$Q_S = \frac{q_r}{q_i}$.~~

r relative retention,

~~$r = \frac{t_2 - t_a}{t_1 - t_a}$~~

$$r = \frac{t_2 - t_M}{t_1 - t_M}$$

r_i peak response of an impurity obtained from a chromatogram.

~~r_i~~, r_{IS} peak response of the internal standard obtained from a chromatogram. ■1S (*USP29*)

r_S peak response of the Reference Standard obtained from a chromatogram.

r_U peak response of the analyte obtained from a chromatogram.

R resolution between two chromatographic peaks,

$$R = \frac{2(t_2 - t_1)}{W_1 + W_2}$$

■ or $R = \frac{2(t_2 - t_1)}{1.70(W_{1,h/2} + W_{2,h/2})}$ ■1S (*USP29*)

R_F chromatographic retardation factor equal to the ratio of the distance from the origin to the center of a zone divided by the distance from the origin to the solvent front.

~~R_r~~ ~~relative retention~~

~~$R_r = \frac{\text{distance traveled by test substance}}{\text{distance traveled by standard}}$.~~

■■1S (*USP29*)

~~R_r~~ relative retention time

■R_r■1S (*USP29*)

$$R_r = \frac{t_2}{t_1}$$

■R_{rel} relative retardation

$$R_{rel} = \frac{\text{distance traveled by test substance}}{\text{distance traveled by standard}}$$ ■1S (*USP29*)

R_S peak response ratio for a Standard preparation containing Reference Standard and internal standard,

~~$R_S = \frac{r_s}{r_i}$~~

■$R_S = \frac{r_S}{r_{IS}}$ ■1S (*USP29*)

R_U peak response ratio for *Assay preparation* containing the analyte and internal standard,

~~$R_U = \frac{r_U}{r_i}$~~

■$R_U = \frac{r_U}{r_{IS}}$ ■1S (*USP29*)

S_R (%) relative standard deviation in percentage,

$$S_R\,(\%) = \frac{100}{\bar{X}}\left[\frac{\sum_{i=1}^{N}(X_i - \bar{X})^2}{N - 1}\right]^{1/2}$$

where X_i is an individual measurement in a set of N measurements and X is the arithmetic mean of the set.

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T tailing factor,

$$T = \frac{W_{0.05}}{2f}$$

t retention time measured from time of injection to time of elution of peak maximum.
t_a retention time of nonretarded component, air with thermal conductivity detection.
W width of peak measured by extrapolating the relatively straight sides to the baseline.
$W_{h/2}$ width of peak at half height.
$W_{0.05}$ width of peak at 5% height.

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~~

▲1.7▲*USP30*
to 10 µm in diameter,

■or a monolithic silica rod.■1S *(USP29)*

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~~

▲1.7▲*USP30*
to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, ■3 to■1S *(USP28)* 10 µm in diameter.

L9—~~10 µm~~

■■1S *(USP29)*
Irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating,

■3 to 10 µm in diameter.■1S *(USP29)*

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~~

▲1.7▲*USP30*
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 ■■1S *(USP28)* having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating, ■5 to 10 µm in diameter.■1S *(USP28)*

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~~

■[NOTE—Available as YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. and distributed by Waters Corp. (www.waters.com).]■1S *(USP29)*

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~~

■3■1S *(USP29)*
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 YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■ and distributed by Waters Corp. (www.waters.com).■1S *(USP29)*~~

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L31—A

■hydroxide-selective,■1S (*USP29*)
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 by molecular size over a range of 4000 to 500,000 Da. It is spherical, silica-based, and processed to provide pH stability.[6]

■[NOTE—Available as TSKgel G4000 SWXL from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

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, 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, ■about■1S (*USP28*) 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.[7]

■[NOTE—Available as CarboPac MA1 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

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]

■[NOTE—Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.]■1S (*USP29*)

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]

■[NOTE—Available as OmniPac PAX-500 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.[10]

■[NOTE—Available as Chiralpak AD from Chiral Technologies, Inc., ■(www.chiraltech.com).■1S (*USP28*)]■1S (*USP29*)

L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.[11]

■[NOTE—Available as TSK IC SW Cation from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column. [12]

■[NOTE—Available as IonPac CS14 distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter.[13]

■[NOTE—Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).]■1S (*USP29*)

L55—A strong cation-exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.[14]

■[NOTE—Available as IC-Pak C M/D from Waters Corp. (www.waters.com).]■1S (*USP29*)

L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.[15]

[6] ~~Available as TSKgel G4000 SWXL from ■Tosoh Biosep (www.tosohbiosep.com).■1S (*USP28*)~~

[7] ~~Available as CarboPac MA1 and distributed by Dionex ■Corp. (www.dionex.com).■1S (*USP28*)~~

[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 ■Corp. (www.dionex.com).■1S (*USP28*)~~

[10] ~~Available as Chiralpak AD from Chiral Technologies, Inc., ■(www.chiraltech.com).■1S (*USP28*)~~

[11] ~~Available as TSK IC SW Cation from ■Tosoh Biosep (www.tosohbiosep.com).■1S (*USP28*)~~

[12] ~~Available as IonPac CS14 distributed by Dionex ■Corp.■1S (*USP28*) (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).~~

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■[NOTE—Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem).]■1S (*USP29*)

L57—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å.

■[NOTE—Available as Ultron ES-OVM from Agilent Technologies (www.agilent.com/chem).]■1S (*USP29*)

L58—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.[16]

■[NOTE—Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) www.bio-rad.com.]■1S (*USP29*)

▲L59—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.▲*USP28*[17]

■[NOTE—Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively) (www.tosohbiosep.com).]■1S (*USP29*)

▲L60—Spherical, porous silica gel, 3 or 5 µm in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped.▲*USP28* ~~with acetamidopropyl groups to a ligand density of about 6 µmoles per m²~~[18]

■[NOTE—Available as Supelcosil ABZ from Supelco (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

■L61—A hydroxide-selective, strong anion-exchange resin consisting of a highly cross-linked core of 13-µm microporous particles having a pore size less than 10 Angstrom units and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene with a latex coating composed of 85-nm diameter microbeads bonded with alkanol quaternary ammonium ions (6%).■2S (*USP28*)

■[NOTE—Available as Ion Pac AS-11 and AG-11 from Dionex (www.dionex.com).]■1S (*USP29*)

■L62—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter.■2S (*USP28*)

■L## (Dalteparin Sodium, anion-exchange Dowex 1X8)—[To come.]

L## (Dalteparin Sodium, cation-exchange Dowex 50WX2)—[To come.]■1S (*USP29*)

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.~~

■[NOTE—Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.]■1S (*USP29*)

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.[19]

■[NOTE—A suitable grade is available commercially as ''SP2100/0.1% Carbowax 1500'' from Supelco, Inc. (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

G39—Polyethylene glycol (av. mol. wt. about 1500).
G40—Ethylene glycol adipate.
G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).

[16] ~~Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) (www.bio-rad.com).~~

[17] ~~Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively). (www.tosohbiosep.com).~~

[18] ~~Available as Supelcosil ABZ from Supelco. (www.sigma-aldrich.com/supelco).~~

[19] ~~A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc., ■~~(www.sigma-aldrich.com/supelco).■1S *(USP28)*

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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.[20]~~

■■1S (*USP29*)

▲G## (Docosahexaenoic acid, Famewax)—Polyethylene glycol, cross-linked (average molecular weight of not more than 20,000).

G## (Tetrafluoroethane, Bentone 34/SP-1200)—Aluminosilicate montmorrillonite that has been treated with dimethyloctadecylammonium salts plus a low polarity ester phase.

G## (Tetrafluoroethane, Krytox)—A perfluorinated polyether fluid.▲*USP30*

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[21]

■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)
to mask surface silanol groups.
S1AB—The siliceous earth as described above is both acid- and base-washed.[21]

■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)
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.[22]

■[NOTE—Commercially available as SP1500 on Carbopack B from Supelco (www.sigma-aldrich.com/supelco).]■1S (*USP29*)
S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

▲S## (Tetrafluoroethene, Porapak T)—Polymer based on highly polar ethylene glycol dimethacrylate monomer, with a surface area of 225–350 m^2 per g.▲*USP30*

BRIEFING

〈**711**〉 **Dissolution,** *USP 28* page 2412 and page 3572 of the *Second Supplement.* In the introductory paragraph, it is proposed to remove the statement on interchangeability. Although this chapter is harmonized by agreement among the European Pharmacopoeia, the Japanese Pharmacopoeia, and the United States Pharmacopeia, regulatory interchangeability is currently under consideration by the working group Q4B of the International Conference on Harmonization. It is further proposed, in *Apparatus 1 and Apparatus 2* in the *Procedure* section, to add the subsection *Procedure for a Pooled Sample for Immediate-Release Dosage Forms.* Finally, it is proposed to include, in the *Interpretation* section, the procedure and acceptance table for a pooled sample of immediate-release dosage forms in the USP-specific text of this harmonized general test chapter. Concern has been expressed by stakeholders that the pre-

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[20] ~~A suitable grade is available commercially as "Optima Delta-3" from Machery-Nagel, Inc., 215 River Vale Road, River Vale, NJ 07675.~~
[21] ~~Unless otherwise specified in the individual monograph, silanized support is intended.~~
[22] ~~Commercially available as SP1500 on Carbopack B from Supelco (www.sigma-aldrich.com/supelco).~~

viously proposed removal of this text from the chapter, and inclusion separately in each affected drug product monograph, will cause an unnecessary burden on their resources. Therefore the Biopharmaceutics Expert Committee has proposed this revision. At this time, the committee does not envision an expansion of the number of monographs for which pooled sampling is specified. The monographs in which pooled sampling appears represent well-characterized dosage forms with long product histories. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2006, the same date as the date of implementation of the harmonized chapter.

(BPC: W. Brown) RTS—42348-1; 42761-1

Change to read:

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* ~~The texts of these pharmacopeias are therefore interchangeable, and the methods of the European Pharmacopoeia or the Japanese Pharmacopoeia may be used for demonstration of compliance instead of the present general chapter.~~

•.[2]

These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.

This test is provided to determine compliance with the dissolution requirements ◆where stated in the individual monograph◆ for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. ◆Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for *Delayed-Release Dosage Forms* is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

USP Reference Standards ⟨11⟩—*USP Chlorpheniramine Maleate Extended-Release Tablets RS (Drug Release Calibrator, Single Unit). USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS (Dissolution Calibrator, Nondisintegrating).*◆

Change to read:

PROCEDURE

Apparatus 1 and Apparatus 2

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the specified apparatus ◆given in the individual monograph,◆ assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate ◆given in the individual monograph.◆ Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis ◆as directed in the individual monograph◆ using a suitable assay method.[3] Repeat the test with additional dosage form units.

If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary.

Dissolution Medium—A suitable dissolution medium is used. Use the solvent specified ◆in the individual monograph.◆ The volume specified refers to measurements made between 20° and 25°. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH ◆given in the individual monograph.◆ [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.[4]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

•◆Procedure for a Pooled Sample for Immediate-Release Dosage Forms—Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed in *Procedure* for *Apparatus 1 and Apparatus 2* in *Immediate-Release Dosage Forms.* Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the

[3] Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

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pooled sample as the test specimen. Determine the average amount of the active ingredient dissolved in the pooled sample.◆●[2]

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms.*

Time—The test-time points, generally three, are expressed in hours.

DELAYED-RELEASE DOSAGE FORMS

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

Use *Method A* or *Method B* and the apparatus specified ◆in the individual monograph.◆ All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate ◆given in the monograph.◆

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—Complete the operations of adding the buffer and adjusting the pH within 5 minutes.]

With the apparatus operating at the rate specified ◆in the monograph,◆ add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph.◆ At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for the minimum amount dissolved is met at an earlier time.◆

Method B—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified ◆in the monograph.◆ After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3 : 1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.]

Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph.◆ At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.◆

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

IMMEDIATE-RELEASE DOSAGE FORMS

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 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 3*.

Dissolution Medium—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

DELAYED-RELEASE DOSAGE FORMS

Proceed as described for *Delayed-Release Dosage Forms, Method B* under *Apparatus 1 and Apparatus 2* using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

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Apparatus 4 (Flow-Through Cell)

IMMEDIATE-RELEASE DOSAGE FORMS

Place the glass beads into the cell specified ◆in the monograph.◆ Place 1 dosage 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.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4*.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2,* using the specified media.

Time—Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Change to read:

INTERPRETATION

Immediate-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph,◆ the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 1*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient ◆specified in the individual monograph,◆ expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in *Acceptance Table 1* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q – 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

◆●Immediate-Release Dosage Forms Pooled Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

◆●[2]

Extended-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph,◆ the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. 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 spec-

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ified fractional dosing interval. Where more than one range is specified ◆in the individual monograph,◆ the acceptance criteria apply individually to each range.

Acceptance Table 2

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.

Delayed-Release Dosage Forms

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA.

Acid Stage—Unless otherwise specified ◆in the individual monograph,◆ the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 3

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units (A_1 + A_2) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units (A_1 + A_2 + A_3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—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 4*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 4* is 75% dissolved unless otherwise specified ◆in the individual monograph.◆ The quantity, Q, ◆specified in the individual monograph◆ is the total amount of active ingredient dissolved in both the *Acid* and *Buffer Stages*, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in *Acceptance Table 4* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units (B_1 + B_2) is equal to or greater than Q, and no unit is less than Q – 15%.
B_3	12	Average of 24 units (B_1 + B_2 + B_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1217**⟩ **Tablet Breaking Force.** This proposed new general information chapter considers tablet friability, hardness, crushing strength, breaking force, and issues that must be considered in the analytical determination of tablet breaking force. The use of breaking force to compute the tensile strength of flat-faced, round tablets is also discussed.

(PDF: W. Brown) RTS—42837-1

Add the following:

▲⟨1217⟩ TABLET BREAKING FORCE

INTRODUCTION

There are a variety of presentations for tablets as delivery systems for pharmaceutical agents, such as rapidly disintegrating, slowly disintegrating, eroding, chewable, and lozenge. Each of these presentations places a certain demand on the bonding, structure, and integrity of the compressed matrix. Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users (patients/consumers). Manufacturing processes such as coating, packaging, and printing can involve considerable stresses, which the tablets must be able to withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. Tablet strength serves both as a criterion by which to guide product development and as a quality control specification.

One commonly employed test of the ability of tablets to withstand mechanical stresses determines their resistance to chipping and surface abrasion by tumbling them in a rotating cylinder. The percentage weight loss after tumbling is referred to as the *friability* of the tablets. Standardized methods and equipment for testing friability have been provided in general chapter *Tablet Friability* ⟨1216⟩.

Another measure of the mechanical integrity of tablets is their *breaking force,* which is the force required to cause them to fail (i.e., break) in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in that plane.

The breaking force of tablets is commonly called *hardness* in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term *hardness* refers to the resistance of a surface to penetration or indentation by a small probe. The term *crushing strength* is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately than does *hardness,* it implies that tablets are actually crushed during the test, which often is not the case. Moreover, the term *strength* in this application can be questioned, because in the physical sciences that term is often used to describe a stress (e.g., tensile strength). Thus, the term *breaking force* is preferred and will be used in the present discussion.

TABLET BREAKING FORCE DETERMINATIONS

Early measuring devices were typically hand operated. For example, the Monsanto (or Stokes) hardness tester was based on compressing tablets between two jaws via a spring gauge and screw. In the Pfizer hardness tester, the vertically mounted tablet was squeezed in a device that resembled a pair of pliers. In the Strong Cobb hardness tester, the breaking load was applied through the action of a small hydraulic pump that was first operated manually but was later motorized. Problems associated with these devices were related to operator variability in rates of loading and difficulties in proper setup and calibration. Modern testers employ mechanical drives, strain gauge–based load cells for force measurements, and electronic signal processing, and therefore are preferred. However, several important issues must be considered when using them for the analytical determination of breaking force; these are discussed below.

Platens

The platens should be parallel. Their faces should be polished smooth and precision-ground perpendicularly to the direction of movement. Perpendicularity must be preserved during platen movement, and the mechanism should be free of any bending or torsion displacements as the load is applied. The contact faces must be larger than the area of contact with the tablet.

Rate and Uniformity of Loading

Either the rate of platen movement or the rate at which the compressive force is applied (i.e., the loading rate) should be constant. Maintaining a constant loading rate avoids the rapid buildup of compressive loads, which may lead to uncontrolled crushing or shear failure and greater variability in the measured breaking force. However, constant loading rate measurements may be too slow for real time monitoring of tablet production.

The rate at which the compressive load is applied can significantly affect results, because time-dependent processes may be involved in tablet failure (*1*). How a tablet matrix responds to differences in the loading rate depends on the mechanism of failure. At low strain rates, some materials may fail in a ductile manner, but brittle failure is more likely at faster strain rates. The transition from ductile to brittle failure is accompanied by an increase in the breaking force. Devices that simply crush tablets may produce deceptively reproducible data because they lack sensitivity.

A constant loading rate of 20 newtons (N) or less per second or a constant platen movement of 3 mm or less per second encourages controlled breaking in a consistent manner. To ensure comparability of results, testing must occur under identical conditions of loading rate or platen movement rate. Since there are certain advantages to each system of load application, both are found in practice. Because the particular testing situation and the type of tablet matrix being evaluated will pose different constraints, there is also no basis to declare an absolute preference for one system over the other. This general chapter proposes consideration of both approaches.

Method A: Constant rate of load application. The breaking force (at point of matrix failure) determined with a uniform rate of force application at a rate of 20 N or less per second.

Method B: Constant rate of displacement. The breaking force (at point of matrix failure) determined with force application coming from a uniform platen movement at a rate of 3 mm or less per second.

The different methods may lead to numerically different results for a particular tablet sample, requiring that the rate of load application or displacement must be specified along with the determined breaking force.

Dependence of Breaking Force on Tablet Geometry and Mass

Measurements of breaking force do not take into account the dimensions or shape of the tablet. Thicker tablets of the same material compressed under conditions identical to those of thinner tablets, with the same tooling shape and to the same peak force, will require greater breaking forces. For direct comparisons (i.e., without any normalizations of the data), breaking force measurements should be performed on tablets having the same dimensions and geometry.

Tablet Orientation

Tablet orientation in diametral compression of round tablets without any scoring is unequivocal. That is, the tablet is placed between the platens so that compression occurs across a diameter. However, tablets with a unique or complex shape may have no obvious orientation for breaking force determination. Because the breaking force may depend on the tablet's orientation in the tester, to ensure comparability of results, it is best to settle on a standard orientation, preferably one that is most readily and easily reproduced by operators. In general, tablets are tested either across the diameter or at 90° to the longest axis. Scored tablets have two orientation possibilities. When they are oriented with their scores perpendicular to the platen faces, the likelihood that tensile failure will occur along the scored line increases. This provides information about the strength of the matrix at the weakest point in the structure. When scored tablets are oriented with their scores parallel to the platen faces, more general information about the strength of the matrix is derived.

Capsule-shaped tablets or scored tablets may best be broken in a three-point flexure test (*2*). A fitting, which is either installed on the platens or substituted for the platens, supports the tablet at its ends and permits the breaking load to be applied to the opposite face at the unsupported midpoint of the tablet. The fittings are often available from the same source that supplies the hardness tester.

Units, Resolution, and Calibration

Modern breaking force testers are usually calibrated in kiloponds or newtons. The relationship between these units of force (*3*) is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.80 N. Some breaking force testers also will provide a scale in Strong Cobb units (SCU), a carryover from the days when Strong Cobb hardness testers were in common usage. The conversion between SCU and N or kp must be viewed with caution, because the SCU is derived from a hydraulic device and is a pressure.

Generally, contemporary breaking force testers use modern electronic designs with digital readouts. Some units also have an integral printer or may be interfaced with a printer. Breaking forces should be readable to within 1 N.

Breaking force testers should be calibrated periodically. The force sensor as well as the mechanics of the apparatus needs to be considered. For the force sensor, the complete measuring range (or, at a minimum, the range used for measuring the test sample) should be calibrated to a precision of 1 N, using either the static or dynamic method. Static calibration generally employs traceable counterweights; at least three different points are checked to assess linearity. Dynamic calibration makes use of a traceable reference-load cell that is compressed between the platens. The functional calibration of a breaking force test apparatus should also confirm that the velocity and the constancy of velocity for load application or displacement are within prescribed tolerances throughout the range of platen movement.

Sample Size

In order to achieve sufficient statistical precision for the determination of average breaking force, a minimum of 6 tablet samples should be tested. The average breaking force alone may be adequate to fulfill the purpose of process or product quality control. In cases where breaking force may be particularly critical, the average plus individual breaking force values should be accessible.

TENSILE STRENGTH

The measurement of tensile strengths provides a more fundamental measure of the mechanical strength of the compacted material and takes into account the geometry of the tablet. If tablets fail in tension, the breaking force can be used to calculate the tensile strength. Unfortunately, this is practical only for simple shapes. If flat-faced round tablets (right circular cylinders) fail in tension, as indicated by a clean split into halves under diametral compression, the breaking force may be used to compute the tensile strength from the following equation (*4*), which applies only to cylindrical tablets:

$$\sigma_X = \frac{2F}{\pi DH}$$

in which σ_X is the tensile strength, F is the breaking force, D is the tablet diameter, and H is the tablet thickness. Because only tablets that fail in tension are counted, the data are based on tablets that fail in a consistent way. Thus, reproducibility of data should be enhanced when compared to conventional breaking-strength testing. Moreover, the data will be normalized with respect to tablet dimensions, because both diameter and thickness are included in the equation. The derivation of this equation may be found in standard texts (*5, 6*); it is based on elastic theory and the following assumptions:

1. The tablet is an isotropic body
2. Hooke's law is obeyed
3. The modulus of elasticity in compression and in tension is the same
4. Ideal point loading occurs

The derivation has been extended to convex-faced tablets (*7, 8*):

$$\sigma_X = \frac{10F}{\pi D^2}\left[\frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01\right]^{-1}$$

where σ_X is the tensile strength, F is the breaking force, D is the tablet diameter, H is the tablet thickness, and W is the central cylinder thickness (tablet wall height).

The slow and constant loading rate of modern motorized break force testers encourages tensile failure. However, ideal point loading may not occur, because of crushing and the induction of shear failure at the interface with the surface of the platens. The addition of padding to the platens helps prevent shear at contact points and promotes true tensile failure. On that basis, padding is strongly recommended when highly precise measurements are needed. Padding should be relatively thin so that any deviation from the assumption of true point-source force application will not be large. The padding should also collapse very easily so that its deformation does not become part of the force measured by the test apparatus. In more routine settings involving measurements on a large number of samples, the addition of padding could contribute to inaccuracies in measurement as powder from previously tested samples becomes embedded in the collapsible matrix and thereby alters its properties. Unless provisions for frequent and routine replacement of the padding are made, it can be considered acceptable to ignore the use of padding material to maintain constancy of the test conditions.

Bending or flexure of tablets is another option for determining the tensile strength of tablets. Under ideal loading conditions, a breaking load applied to the unsupported midpoint of one face will result in the generation of pure tensile

stress in the opposite face. If the tablets are right circular cylinders and are subjected to three-point flexure, the tensile strength may be estimated using the following equation (*9*):

$$\sigma_X = \frac{3FL}{2H^2D}$$

in which L is the distance between supports, and the other terms are as defined above. The assumptions are the same as those for calculating tensile strength from diametral compression. However, tensile strengths determined by flexure and diametral compression may not agree, because of likely nonideal loading and the induction of shear failure during testing.

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9. Pitt, K.G.; Newton, J.M.; Richardson, R.; Stanley, P. The material tensile strength of convex-faced aspirin tablets. *J. Pharm. Pharmacol.* **1989,** *41,* 289–292.▲*USP30*

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Geneticin. This new reagent is used in the test for *Bioidentity* in the monograph for *Glucagon,* proposed elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—43070-2

Add the following:

▲**Geneticin** *(G418; O-2-Amino-2,7-dideoxy-D-glycero-alpha-D-glucoheptopyranosyl-(1-4)-O-(3-deoxy-4-C-methyl-3-(methylamino)-beta-L-arabinopyranosyl-(1-6)-D-streptamine),* $C_{20}H_{40}N_4O_{10}$—**496.55** [*49863-47-0*]—Use a suitable grade, cell culture tested.▲*USP30*

In-Process Revision

BRIEFING

Hydroxypropyl-β-cyclodextrin. It is proposed to add this new reagent used in the *Related compounds* test in the monograph for *Levocabastine Hydrochloride* published elsewhere in this issue of *PF*.

(HDQ: M. Marques) RTS—43014-2

Add the following:

▲**Hydroxypropyl-β-cyclodextrin,** (*Hydroxypropylbetadex*), $C_{42}H_{70}O_{35}(C_3H_6O)_x$ with x = 7 molar substitution—[*94035-02-6]*—Use a suitable grade with a molar substitution not less than 0.40 and not more than 1.50.▲*USP30*

BRIEFING

Isopropyl Iodide *(2-Iodopropane), USP 28* page 2823. It is proposed to update the information about this compound.

(HDQ: M. Marques) RTS—43120-2

Change to read:

Isopropyl Iodide (*2-Iodopropane*), C_3H_7I—**169.99**~~—Colorless liquid, discoloring upon exposure to air and light. Sparingly soluble in water; miscible with alcohol, with benzene, with chloroform, and with ether.~~

~~*Density:* between 1.696 and 1.704.~~

~~*Refractive index* ⟨831⟩: between 1.4987 and 1.4997 at 20°.~~

▲[*75-30-9*]—Use a suitable grade.▲*USP30*

BRIEFING

Sodium Carbonate, Monohydrate. It is proposed to add this new reagent.

(HDQ: M. Marques) RTS—43228-1

Add the following:

▲**Sodium Carbonate, Monohydrate,** $Na_2CO_3.H_2O$—**124.00** [*5968-11-6*]—Use ACS reagent grade.▲*USP30*

BRIEFING

1-Vinyl-2-pyrrolidone, *USP 28* page 2850 and page 108 of *PF* 31(1) [Jan.–Feb. 2005]. It is proposed to update the information about possible suppliers of this compound.

(HDQ: M. Marques) RTS—42795-2

Change to read:

~~**1-Vinyl-2-pyrrolidone**~~

▲**Vinylpyrrolidinone** (*1-Vinyl-2-pyrrolidinone, 1-Vinyl-2-pyrrolidone, N-Vinylpyrrolidinone, N-Vinylpyrrolidone*).▲*USP30*

C_6H_9NO—**111.14**

▲[*88-12-0*]▲*USP30*

—Colorless liquid.

Assay—Inject an appropriate volume into a 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 0.25-mm × 30-m capillary column coated with a 1-µm layer of G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the C_6H_9NO peak is not less than 99.0% of the total peak area.

Water, Method I ⟨921⟩: not more than 0.1%, determined on 2.5 g, using a mixture of 50 mL of methanol and 10 mL of butyrolactone as the solvent.

▲[NOTE—A suitable grade is available from ~~http://www.sigma-aldrich.com, catalog number V340-9.~~ Merck KGaA/ EMD chemicals, catalogue number 8.08518.0250, www.emdchemicals.com.]▲*USP30*

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 28* page 2869, page 3639 of the *Second Supplement,* and page 1490 of *PF* 31(5) [Sept.–Oct. 2005].

(HDQ) RTS—39955-1; 42796-1

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 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:	
■Benazepril Tablets	W■1S (*USP29*)
Add the following:	
■Citalopram ~~Hydrobromide~~ Tablets	W■1S (*USP29*)
Add the following:	
■Black Cohosh Tablets	T, LR■1S (*USP29*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W■1S (*USP29*)
Add the following:	
■Diclofenac Potassium Tablets	T, LR■2S (*USP29*)
Add the following:	
■Didanosine Tablets	T■2S (*USP29*)
Add the following:	
▲Estradiol Vaginal Tablets	T▲*USP30*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W■1S (*USP29*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W■1S (*USP29*)
Add the following:	
■Fosinopril Sodium Tablets	T■1S (*USP29*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T■1S (*USP29*)
Add the following:	
■Ginkgo Capsules	T, LR■1S (*USP29*)
Add the following:	
■Ginkgo Tablets	T, LR■1S (*USP29*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■■1S (*USP29*)
Add the following:	
▲Glipizide and Metformin Hydrochloride Tablets	W▲*USP30*
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR■1S (*USP29*)
Add the following:	
■Irbesartan Tablets	W■1S (*USP29*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP29*)

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Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S (*USP29*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■1S (*USP29*)
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■2S (*USP29*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S (*USP29*)
Add the following:	
▲Methscopolamine Bromide Tablets	T▲*USP29*
Add the following:	
■Modafinil Tablets	T■1S (*USP29*)
Add the following:	
■Nefazodone Hydrochloride Tablets	T■2S (*USP29*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S (*USP29*)
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■2S (*USP29*)
Add the following:	
■Quinapril Tablets	W■1S (*USP29*)
Add the following:	
■Tizanidine Tablets	T■1S (*USP29*)
Add the following:	
■Valerian Capsules	T, LR■1S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■1S (*USP29*)
Add the following:	
▲Zinc Sulfate Tablets	W▲*USP29*

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 28* page 2875, page 3640 of the *Second Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], and page 1491 of *PF* 31(5) [Sept.–Oct. 2005].

(HDQ) RTS—42243-1; 42382-1; 42382-4; 42382-5; 42740-1; 42982-1; 43026-1

Add the following:

▲**Canola Oil:** Clear, pale yellow, slightly viscous liquid. Practically insoluble in water and in alcohol; miscible with light petroleum (bp: 40° to 60°). *NF category:* Solvent; vehicle (oleaginous).▲*NF25*

Add the following:

▲**Synthetic Conjugated Estrogens:** A white to light buff, crystalline or amorphous powder that is odorless or has a slight odor.▲*USP30*

In-Process Revision

Delete the following:

▲~~**Diphtheria Toxin for Schick Test:** Transparent liquid.~~▲*USP30*

Add the following:

▲**Oleyl Oleate:** Clear, colorless to light yellow liquid. Has a faint characteristic odor. Slightly soluble in alcohol; miscible with chloroform and with ether. *NF category:* Emollient; emulsifying and/or solubilizing agent.▲*NF25*

Add the following:

▲**Risperidone:** White or almost white powder. Soluble in methylene chloride; sparingly soluble in ethanol; practically insoluble in water.▲*USP30*

Delete the following:

▲~~**Rubella and Mumps Virus Vaccine Live:** Solid having the characteristic appearance of substances dried from the frozen state. The Vaccine is to be constituted with a suitable diluent just prior to use. Constituted vaccine undergoes loss of potency on exposure to sunlight.~~▲*USP30*

Delete the following:

▲~~**Schick Test Control:** Transparent liquid.~~▲*USP30*

In-Process Revision

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 31(1) through 31(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF*.

Title and Proposal	***PF Volume, Issue, and Page Numbers of Pending Proposals***		
	Vol.	***No.***	***Page(s)***
General Notices—*Tests and Assays—Foreign Substances and Impurities; Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs* (*Controlled Cold Temperature*-added)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Oral Suspension—*USP Reference standards [USP4-Aminophenol RS]* (add), *Limit of 4-aminophenol* (add)	30	5	1579
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets— *Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Dissolution, Assay*	31	3	726
Alendronate Sodium—*Packaging and storage*	31	5	1344
Allopurinol—*USP Reference standards, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride—*Chromatographic purity*	31	5	1344
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Amphetamine Sulfate—*Assay*	31	2	381
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspartic Acid—*Chloride*	31	5	1345
Aspirin Boluses—*Dissolution*	31	4	1026
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Atenolol—*Assay*	31	5	1345
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Tablets—*Dissolution*	30	1	61
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	29	3	606
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Betamethasone Tablets—*Dissolution*	30	1	62
Betamethasone Acetate—*Identification B*	31	2	381
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bromocriptine Mesylate—*Chromatographic purity*	31	5	1346
Budesonide (new)	30	6	1978
Bupropion Hydrochloride—*Chromatographic purity*	31	2	381

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Bupropion Hydrochloride Extended-Release Tablets—*USP Reference standards, Related compounds*	31	2	384
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Butorphanol Tartrate Nasal Solution (new)	31	5	1346
Calcitonin Salmon (new)	31	4	1036
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	29	5	1433
Calcitriol Injection (new)	29	5	1434
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Camphor—*Water*	31	3	742
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Suspension (new)	30	3	812
Cefaclor Tablets (new)	29	6	1858
Cefadroxil for Oral Suspension—*Water*	31	4	1045
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Ciprofloxacin—*USP Reference standards, Other requirements*	31	2	393
Ciprofloxacin Injection—*Definition, USP Reference standards, Pyrogen* (delete), *Bacterial endotoxins* (add)	31	2	393
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	4	1046
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid*	31	2	394
Cladribine (new)	31	2	395
Clindamycin Hydrochloride Oral Solution—*pH*	31	5	1350
Clotrimazole Lozenges—*Disintegration* (delete), *Dissolution* (add)	31	2	398
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Colchicine Tablets—*Dissolution*	30	1	91
Cyanocobalamin—*Pseudo cyanocobalamin*	31	5	1350
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Dibucaine—*Identification B*	31	2	399
Dibucaine Cream—*Identification, Assay*	31	2	399

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Dibucaine Ointment—*Identification*	31	2	400
Dibucaine Hydrochloride—*Labeling* (add), *USP Reference standards, Identification B, Other requirements* (add)	31	2	400
Dibucaine Hydrochloride Injection—*Identification A*	31	2	401
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	31	5	1355
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	31	5	1359
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Digoxin Oral Solution—*Assay*	31	5	1361
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add), *Assay*	29	6	1870
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Divalproex Sodium (new)	31	5	1362
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dorzolamide Hydrochloride—*Limit of dorzolamide hydrochloride related compound A, Assay*	31	2	401
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Drospirenone (new)	31	3	754
Dyclonine Hydrochloride—*Identification B*	31	1	42
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*USP Reference standards*	31	5	1363
Epinephrine Injection—*Identification A, B*	31	1	43
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Conjugated Estrogens—*Definition*	30	3	840
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	4	1067
Ethosuximide Capsules—*Dissolution*	30	1	102
Ethyl Chloride—*Alcohol* (delete)	31	5	1368
Fenofibrate (new)	31	3	763
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Melting range* (delete), *Related compounds*	31	5	1368
Fluorometholone Acetate (new)	31	5	1371
Fluoxetine Delayed-Release Capsules (new)	30	3	849
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propianate—*Chemical information, Definition, Content of acetone, Assay*	31	4	1070
Fluticasone Propianate Nasal Spray (new)	31	4	1071
Fluvoxamine Maleate Tablets (new)	30	5	1622
Fosinopril Sodium (new)	30	6	2001
Fosinopril Sodium Tablets (new)	30	6	2004

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Gabapentin Capsules (new)	28	7	298
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification, Dissolution*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	2	410
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Helium—*USP Reference standards* and *Assay* (postponed indefinitely)	31	4	1014
Helium—*Definition, Packaging and storage*	31	4	1077
Hydrocodone Bitartrate—*USP Reference standards [USP Hydrocodone Bitartrate Related Compound A RS], Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hyoscyamine Sulfate Elixir—*Identification*	31	5	1372
Hyoscyamine Sulfate Injection—*Identification*	31	5	1373
Hyoscyamine Sulfate Oral Solution—*Identification*	31	5	1373
Hyoscyamine Sulfate Tablets—*Identification*	31	5	1374
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Ibuprofen—*Assay*	31	5	1374
Indocyanine Green—*Definition, Assay*	29	6	1905
Insulin—*USP Reference standards*	31	5	1375
Insulin Human—*USP Reference standards*	31	5	1375
Iodixanol—*Labeling* (add), *USP Reference standards, Limit of calcium, Other requirements* (add)	31	1	54
Irbesartan Tablets (new)	31	4	1080
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isopropyl Alcohol—*USP Reference standards* (add), *Identification*	31	5	1375
Isosorbide Dinitrate Tablets—*Dissolution, Assay*	31	5	1375
Isosorbide Dinitrate Chewable Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Extended-Release Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Sublingual Tablets—*Dissolution, Assay*	31	5	1377
Diluted Isosorbide Mononitrate—*pH*	31	4	1060
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lidocaine Hydrochloride—*Assay*	31	2	415
Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	31	2	415
Lipid Injectable Emulsion (new)	31	2	416
Lisinopril Tablets—*Dissolution*	31	4	1090
Lithium Carbonate Extended-Release Tablets—*Dissolution*	31	5	1385
Loratadine Oral Solution—*Antimicrobial effectiveness test* (delete)	31	1	56
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919

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Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	31	5	1386
Magnesium Chloride—*Identification, Insoluble matter*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mannitol Injection—*Labeling*	28	1	73
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Mefloquine Hydrochloride—*Related compounds*	31	4	1091
Megestrol Acetate Oral Suspension—*Dissolution*	31	5	1387
Meloxicam (new)	31	1	57
Meperidine Hydrochloride—*Packaging and storage, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	62
Meprobamate Tablets—*Dissolution*	30	1	129
Mesalamine—*Related compounds*	31	2	424
Metformin Hydrochloride—*Packaging and storage* (add), *Related compounds*	31	4	1092
Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methenamine Tablets—*Dissolution*	30	1	130
Methenamine Hippurate Tablets—*Labeling* (add), *Dissolution*	31	1	63
Methocarbamol Tablets—*Dissolution*	30	1	130
Methoxyflurane—*Foreign odor* (delete)	31	5	1388
Methscopolamine Bromide (new)	31	2	425
Methscopolamine Bromide Tablets (new)	31	2	427
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Vaginal Suppositories—*Assay*	31	5	1389
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Nabumetone—*Related compounds*	31	1	63
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nalidixic Acid—*Assay*	30	1	132
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage*	30	4	1264
Nefazodone Hydrochloride (new)	31	4	1094
Nefazodone Hydrochloride Tablets (new)	31	4	1096
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Nitrous Oxide—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1014
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Limit of residual solvents, Chromatographic purity, Assay*	31	5	1390
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100

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Omeprazole Delayed-Release Capsules—*Identification, Chromatographic purity*	31	5	1392
Ondansetron Oral Solution—*Packaging and storage*	30	3	905
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new)	30	4	1276
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Paroxetine Tablets—*Identification A, C*	31	2	435
Paroxetine Hydrochloride—*USP Reference standards, Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine, Chromatographic purity*	31	4	1112
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	72
Pentobarbital Sodium—*Definition, Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piperazine Citrate Tablets—*Dissolution*	30	1	165
PEG 3350 and Electrolytes for Oral Solution—*Title* (name change—*delayed implementation to February 1, 2009*), *Definition, Assay for potassium and sodium*	31	5	1393
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Bromide (new)	31	2	441
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	31	5	1394
Prednicarbate (new)	31	5	1398
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170

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Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Quinapril Tablets—*Packaging and storage*	29	4	1071
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards [USP Ranitidine Resolution Mixture RS], Chromatographic purity, Assay*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	30	6	2036
Oral Rehydration Salts—*USP Reference standards* (add), *Identification F* (delete), *Assay for citrate*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Ritonavir (new)	31	3	788
Saccharin Calcium (new)—*Harmonization*	31	2	607
Saccharin Sodium (new)—*Harmonization*	31	4	1225
Saquinavir Mesylate—*Identification*	31	5	1400
Scopolamine Hydrobromide—*Identification A*	31	1	73
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bicarbonate Injection—*Packaging and storage*	31	5	1401
Sodium Bromide (new)	31	2	446
Sodium Chloride—*Identification, Loss on drying, Limit of phosphates, Limit of potassium*	31	5	1401
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797
Sodium Lactate Injection—*Identification B* (delete)	31	5	1402
Sodium Phosphates Rectal Solution—*Assay*	31	5	1403
Sodium Salicylate Tablets—*USP Reference standards* (add)	31	4	1116
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone Oral Suspension (new)	30	3	929
Spironolactone Tablets—*Assay*	31	1	74
Spironolactone and Hydrochlorothiazide Oral Suspension (new)	30	3	930
Stavudine Capsules—*Assay*	31	5	1403
Succinylcholine Chloride—*Limit of ammonium salts* (delete), *Chromatographic purity*	31	5	1404
Sulfamethazine Granulated—*Assay*	31	3	797
Tazobactam (new)	31	4	1116
Technetium Tc 99m Fanolesomab Injection (new)—*Packaging and storage* (add)	31	5	1405
Terbutaline Sulfate—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	75
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Terbutaline Sulfate Tablets—*USP Reference standards, Dissolution*	31	1	76
Tetracaine Hydrochloride—*Identification A*	31	2	451
Thalidomide—*Chromatographic purity*	31	2	452
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Thioridazine Hydrochloride—*Identification*	31	3	798
Tiagabine Hydrochloride—*Chromatographic purity*	30	5	1649
Tiamulin (new)	31	1	77
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Timolol Maleate Tablets—*Dissolution*	30	1	191

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Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Titanium Dioxide (NL to come)—*New Monograph [UV Attenuation]*	30	4	1304
Tizanidine Tablets (new)	31	2	456
Tizanidine Hydrochloride (new)	31	2	452
Tolazamide—*Chromatographic purity*	31	4	1118
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	31	4	1119
Travoprost Ophthalmic Solution (new)	31	4	1121
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate*	31	2	465
Triclosan—*USP Reference standards; Limit of monochlorophenols and 2,4-dichlorophenol; Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran; Assay*	31	5	1408
Trimethoprim—*Packaging and storage*	31	5	1409
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Tryptophan—*Chloride, Sulfate*	31	5	1410
Tylosin Tartrate (new)	31	5	1410
Ursodiol Capsules—*Dissolution*	31	3	800
Valsartan (new)	29	6	1996
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2007)*	31	5	1412
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127
Purified Water—*Definition*	31	2	467
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins, Oxidizable substances*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Zinc Oxide—*Iron and other heavy metals*	31	1	80
Zinc Oxide Neutral (new)	31	1	80
Zinc Sulfate Oral Solution (new)	31	2	468
Zinc Sulfate Tablets (new)	31	1	82
<u>*Dietary Supplements Monographs*</u>			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811

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Choline Chloride—*Limit of total amines*	31	1	84
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Powdered Ginkgo Extract (new)	27	2	2233
Ginkgo Capsules (new)	27	2	2238
Ginkgo Tablets (new)	27	2	2240
American Ginseng Capsules (new)	30	2	565
American Ginseng Tablets—*Dissolution [to come]*	30	2	567
Asian Ginseng Capsules (new)	30	2	571
Lutein—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1133
Lutein Preparation—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1134
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Psyllium Husk—*Definition, Light extraneous matter, Heavy extraneous matter* (delete)	30	6	2077
Pygeum Extract—*Packaging and storage*	30	3	956
Selenomethionine—*USP Reference standards, Assay*	31	2	482
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian Capsules (new)	27	1	1825
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Packaging, Foreign Matter and Particulates*	31	5	1428
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192

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⟨11⟩ USP Reference Standards—	26	4	1101
	27	1	1832
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	28	3	839
	28	5	1468
	29	3	710
	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
	31	5	1433
⟨41⟩ Weights and Balances—*Introduction, Weights, Balances*	31	2	508
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Procedures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨231⟩ Heavy Metals—*Method II*	31	5	1435
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨281⟩ Residue on Ignition—*Harmonization*	31	5	1526
⟨341⟩ Antimicrobial Agents—Contents—*General Gas Chromatographic Method, Polarographic Method*	30	5	1678
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨386⟩ Environmentally Sensitive Preparations (new)	30	5	1680
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨467⟩ Organic Volatile Impurities—*Title (delayed implementation to January 1, 2007); Residual Solvents Limits; Identification, Control, and Quantification of Residual Solvents; Other Analytical Procedures* (delete); *Appendix 1*	31	5	1435
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Interpretation of Chromatograms, System Suitability, Glossary of Symbols,*	31	3	825
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain-Coated Tablets* (delete)	30	1	234

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	31	5	1448
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨841⟩ Specific Gravity—*Introduction, Method I, Method II* (add)	31	2	515
⟨851⟩ Spectrophotometry and Light-Scattering—*Procedure*	30	5	1703
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new)	31	5	1453
⟨1065⟩ Ion Chromatography (new)	31	2	519
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1075⟩ Good Compounding Practices—*Introduction, Applicable Definitions, Responsibilities of the Compounder, Training, Procedures and Documentation, Drug Compounding Facilities, Drug Compounding Equipment, Component Selection Requirements, Packaging and Drug Product Containers, Compounding Controls, Labeling, Records and Reports, Compounding for a Prescriber's Office Use, Compounding Veterinarian Products, Compounding Pharmacy Generated Products* (delete)	31	1	101
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)	31	5	1463
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1119⟩ Near-Infrared Spectrophotometry—*Instrumentation*	30	6	2137
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)	31	4	1180
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	31	5	1475
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1230⟩ Water for Health Applications—*Microbial Considerations*	31	5	1486
⟨1232⟩ Instrumentation for Analysis of High Purity PharmaceuticalWaters (new)	30	5	1806
⟨2023⟩ Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements—*Supplement Components, Microbiological Testing*	30	5	1818
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
Reagent Specifications			
Acetanilide	31	2	572
Acetyl Chloride	31	2	573
Acetylcholine Chloride	31	2	573
4-Amino-6-chloro-1,3-benzenedisulfonamide	31	2	573

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2-Aminophenol	31	5	1487
3-Aminopropionic Acid	31	4	1189
3-Aminosalicylic Acid	31	5	1487
Amyl Acetate	31	2	574
tert-Amyl Alcohol	31	2	574
Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form	31	3	858
L-Arabinitol (delete)	31	5	1487
L-Asparagine	31	2	574
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (add)	29	1	265
Benzaldehyde	31	2	574
Benzphetamine Hydrochloride	31	2	575
Benzyltrimethylammonium Chloride	31	2	575
Biphenyl	31	2	575
N-Bromosuccinimide	31	2	575
1-Butaneboronic Acid (delete)	31	4	1189
2,3-Butanedione	31	2	576
n-Butyl Chloride	31	2	576
Butyl Methacrylate (add)	31	4	1189
n-Butylboronic Acid	31	4	1189
Cadmium Acetate	31	2	576
Calcium Citrate	31	2	577
Calcium Lactate	31	2	577
Casein	31	2	578
Charcoal, Activated	31	2	578
Chlorobenzene	31	2	578
Congo Red	31	2	578
Cyclohexanol	31	2	579
Deuterated Methanol (new)	29	6	2054
o-Dichlorobenzene	31	2	579
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl	31	3	858
Dicyclohexylamine	31	2	579
Diidofluorescein	31	2	579
DEAE-Agarose (add)	29	1	265
1,2-Dimethoxyethane	31	2	580
2-Dimethylaminoethyl Methacrylate (add)	31	4	1190
N,N-Dimethyldodecylamine-*N*-oxide (add)	27	4	2837
Docusate Sodium (add)	31	4	1190
Dodecyltrimethylammonium Bromide (new)	31	3	859
Erythritol (delete)	31	5	1487
Ethyl Cyanoacetate	31	2	580
Ethylene Glycol	31	2	580
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
Ferric Ammonium Citrate	31	2	581
Furfural	31	4	1190
Galactitol (delete)	31	5	1488
Guaiacol	31	2	581
n-Heptane, Chromatographic	31	2	581
Hexadimethrine Bromide (add)	29	1	265
Hexamethyldisilazane	31	2	581
Hexane, Solvent	31	2	582
Inositol	31	2	582
Isoferulic Acid (add)	27	4	2837
Isopropylamine	31	2	582
Lead Standard Solution (new)	31	5	1488
Magnesium Matrix Modifier (new)	31	5	1488
Maleic Acid	31	2	583
Methyl Acetate	31	2	583
Methyl Red (add)	31	1	108
1-Naphthol	31	2	583
2-Naphthol	31	2	583

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Nitric Acid, 65 Percent (new)	31	5	1488
5-Nitro-1,10-phenanthroline	31	2	584
Nonylphenoxypoly(ethyleneoxy)ethanol	31	2	584
Palladium Matrix Modifier (new)	31	5	1488
Para-aminobenzoic Acid	31	2	584
Paraformaldehyde	31	2	584
Propionic Anhydride	31	2	585
Pyrrole	31	2	585
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Rose Bengal Sodium	31	2	585
Thrombin Human (new)	29	6	2055
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
Silver Oxide	31	2	585
Sodium Arsenite	31	2	586
Sodium Chromate	31	2	586
Sodium Glycocholate	31	2	587
Sodium 1-Hexanesulfonate Monohydrate (new)	31	2	587
Tetramethylammonium Hydroxide	31	2	587
Thioglycolic Acid	31	4	1190
Thymol	31	2	588
n-Tricosane	31	2	588
Triethylamine	31	2	588
2,4,6-Trimethylpyridine	31	2	588
1-Vinyl-2-pyrrolidone	31	1	108
Zinc Sulfate Heptahydrate (add)	26	2	504
Test Solutions			
Phenol TS (new)	31	3	859
Sodium Citrate TS, Alkaline (new)	31	3	859
Sodium Tetraphenylboron TS	31	5	1489
Volumetric Solutions			
Iodine, Hundreth-Normal (0.01 N)	31	5	1489
Lithium Methoxide, Tenth-Normal (0.1 N) in Methanol	31	1	112
Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)	31	5	1490
Reference Tables			
Container Specifications for Capsules and Tablets	31	5	1490
Excipients, USP and NF Excipients, Listed by Category	31	5	1414
Description and Solubility	25	4	8589
	25	6	9254
	26	4	1135
	27	1	1908
	28	2	554
	28	6	1953
	29	1	266
	29	4	1262
	29	5	1684
	30	4	1405
	30	5	1822
	31	1	122
	31	2	591
	31	3	861
	31	4	1193
	31	5	1491
NF Monographs			
Acesulfame Potassium—*Packaging and storage* (add)	31	1	87
Adipic Acid—*Packaging and storage* (add), *USP Reference standards* (add)	31	1	87

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Alfadex—*Packaging and storage*	30	1	202
Amino Methacrylate Copolymer (new)	31	4	1137
Ammonio Methacrylate Copolymer Dispersion—*Identification A, B*	31	2	483
Asparagine—*Packaging and storage* (add), *USP Reference standards, Identification, Chromatographic purity*	31	1	87
Purified Bentonite—*Assay for aluminum and magnesium content*	31	2	483
Butylparaben (new)—*Harmonization*	31	1	191
Calcium Silicate—*Definition, USP Reference standards* (add), *pH, Lead* (delete), *Limit of lead* (add), *Limit of fluoride, Assay for silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	31	5	1417
Carbomer 934—*Labeling*	31	2	484
Carbomer 934 P—*Labeling* (add), *Limit of benzene*	31	2	484
Carbomer 940—*Labeling, Viscosity*	31	2	485
Carbomer 941—*Labeling*	31	2	485
Carbomer 1342—*Labeling*	31	2	485
Carbomer Copolymer—*Definition, Labeling, Limit of benzene* (add), *Organic volatile impurities* (add), *Content of carboxylic acid*	31	2	486
Carbomer Homopolymer (new)	31	2	488
Carbomer Interpolymer—*Labeling, Limit of benzene* (add), *Organic volatile impurities* (add)	31	2	493
Carboxymethylcellulose Calcium—*Heavy metals*	31	5	1420
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity, Heavy metals*	31	5	1420
Cellaburate—*Packaging and storage* (add)	31	5	1420
Microcrystalline Cellulose—*Labeling, Identification, Particle size distribution estimation by analytical sieving*	31	5	1421
Powdered Cellulose—*Identification B*	31	5	1421
Cetostearyl Alcohol—*Assay*	31	2	494
Cetyl Alcohol—*Assay*	31	2	494
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Crospovidone—*Monograph*	28	4	1257
Cyclomethicone—*Identification*	31	4	1140
Dibutyl Sebacate—*Saponification value*	31	4	1140
Diethanolamine—*USP Reference standards* (add), *Identification*	31	5	1422
Diisopropanolamine (new)	31	4	1140
Erythritol (new)	31	5	1422
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Galactose—*Packaging and storage* (add)	31	1	88
Glyceryl Monostearate—*USP Reference standards* (delete), *Hydroxyl value, Saponification value, Assay for monoglycerides*	31	2	495
Purified Honey (new)	31	2	496
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Hydroxypropyl Cellulose—*USP Reference standards* (add), *Identification*	31	5	1425
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isobutane—*Limit of sulfur compounds* (delete)	31	5	1425
Isomalt (new)	31	1	88
Lactitol—*Related compounds*	31	4	1143
Lauroyl Macrogoglycerides (new)	28	4	1212
Lauroyl Polyoxylglycerides (new)	31	1	92
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate—*Harmonization*	30	1	340
Maltitol (new)	31	4	1143
Maltol—*Packaging and storage*	31	5	1425

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Methacrylic Acid Copolymer—*Limit of monomers*	31	1	93
Monoethanolamine—*USP Reference standards* (add), *Identification* (add)	31	5	1425
Neotame (new)	31	2	497
Nitrogen—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1015
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent —*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1015
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Paraffin—*Readily carbonizable substances*	31	5	1426
Phenolsulfonphthalein—*Labeling* (add), *USP Reference standards* (add), *Bacterial endotoxins* (add)	31	1	94
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Organic volatile impurities*	31	1	95
Potassium Alginate (new)	31	5	1426
Propylene Glycol Dilaurate (new)	31	2	500
Propylene Glycol Monolaurate (new)	31	2	501
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618
Sesame Oil—*USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Sodium Caprylate—*Packaging and storage*	30	3	990
Sodium Starch Glycolate—*Harmonization*	31	5	1523
Sodium Sulfite—*Identification*	31	4	1146
Sodium Tartrate—*Packaging and storage*	31	1	95
Rice Starch (new)—*Harmonization*	30	2	721
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Succinic Acid—*Packaging and storage*	31	1	95
Sucralose—*Limit of hydrolysis products*	31	4	1146
Sucrose—*Harmonization*	31	3	902
Compressible Sugar—*Loss on drying*	31	4	1147
Confectioner's Sugar—*Identification*	31	4	1147
Sunflower Oil (new)	31	1	95
Tagatose (new)	30	5	1672
Medium-Chain Triglycerides—*Definition*	31	1	98
Trolamine—*USP Reference standards* (add), *Identification*	31	5	1427
Xylitol—*USP Reference standards, Limit of other polyols, Assay*	31	4	1147

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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USP Monographs			
Acepromazine Maleate—*Labeling, Other requirements*	29	6	1832
Acyclovir—*Labeling, USP Reference standards, Other requirements*	30	5	1580
Adenosine—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Medical Air—*Assay*	28	4	1065
Albendazole Oral Suspension—*Labeling*	29	4	991
Albuterol Tablets—*Assay*	31	1	40
Alcohol—*Harmonization*	30	2	670
Dehydrated Alcohol—*Harmonization*	30	2	673
Alfentanil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1834
Alprostadil—*Labeling, USP Reference standards, Other requirements*	29	5	1412
Alteplase—*Labeling, Other requirements*	29	6	1835
Amifostine—*Labeling, USP Reference standards, Other requirements, Assay*	30	6	1974
Aminocaproic Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Aminopentamide Sulfate—*Labeling, USP Reference standards, Other requirements*	30	4	1163
Aminophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1414
Amitriptyline Hydrochloride—*Labeling, Other requirements*	29	6	1844
Ammonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1415
Ammonium Molybdate—*Labeling, Other requirements*	29	5	1416
Amphotericin B Lotion—*Title*	30	2	444
Amphotericin B Topical Emulsion (entire submission)	30	2	445
Anileridine—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atenolol—*Labeling, USP Reference standards, Other requirements*	29	5	1416
Atracurium Besylate—*Labeling, USP Reference standards, Other requirements*	29	6	1846
Atropine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1847
Aurothioglucose—*Labeling, Other requirements*	29	6	1847
Azaperone—*Labeling, Other requirements*	29	6	1847
Benzoyl Peroxide Lotion—*Title*	30	2	456
Benzoyl Peroxide Topical Emulsion (entire submission)	30	2	456
Benztropine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1848
Benzyl Benzoate Lotion—*Title*	30	2	457
Benzyl Benzoate Topical Emulsion (entire submission)	30	2	457
Betamethasone Tablets—*Identification, Thin-layer chromatographic identification test*	30	1	62
Betamethasone Dipropionate Lotion—*Title*	30	2	458
Betamethasone Dipropionate Topical Emulsion (entire submission)	30	2	459
Betamethasone Valerate Lotion—*Title*	30	2	461
Betamethasone Valerate Topical Emulsion (entire submission)	30	2	461
Bethanechol Chloride—*Labeling, USP Reference standards, Other requirements*	30	5	1586
Biperiden—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Bretylium Tosylate—*Labeling, USP Reference standards, Other requirements*	29	5	1431

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Brompheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1431
Bumetanide—*Labeling, USP Reference standards, Other requirements*	29	5	1432
Bupivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	5	1589
Butorphanol Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1851
Caffeine—*Labeling, USP Reference standards, Other requirements*	30	4	1168
Calcium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1436
Carboprost Tromethamine—*Labeling, USP Reference standards, Other requirements*	30	1	82
Carboxymethylcellulose Sodium—*Harmonization*	28	3	867
Chlordiazepoxide Hydrochloride—*USP Reference standards*	29	6	1859
Chloroprocaine Hydrochloride—*Labeling, Other requirements*	29	5	1438
Chloroquine—*Labeling, USP Reference standards, Other requirements*	29	6	1859
Chlorothiazide—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpheniramine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1439
Chlorpromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1860
Chromic Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Cimetidine—*Labeling, USP Reference standards, Other requirements*	29	5	1440
Ciprofloxacin Hydrochloride—*Labeling, Other requirements*	29	6	1861
Clonidine Hydrochloride Injection (new)—*Preview*	26	2	351
Clotrimazole Lotion—*Title*	30	2	473
Clotrimazole Topical Emulsion (entire submission)	30	2	474
Codeine Phosphate—*Labeling, USP Reference standards, Other requirements*	30	5	1597
Cortisone Acetate—*Labeling, Other requirements*	29	5	1447
Cupric Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1864
Cupric Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1447
Deslanoside—*Labeling, Other requirements*	29	5	1448
Desmopressin Acetate (new)—*Preview*	24	2	5773
Desmopressin Injection (new)—*Preview*	24	2	5778
Desmopressin Nasal Spray Solution (new)—*Preview*	24	2	5779
Desoxycorticosterone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1456
Desoxycorticosterone Pivalate—*Labeling, USP Reference standards, Other requirements*	29	6	1865
Dexamethasone Acetate—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Dextran 1—*Other requirements*	29	6	1866
Dextran 40—*Other requirements*	29	6	1866
Dextran 70—*Other requirements*	29	6	1868
Dextrose—*Labeling, USP Reference standards, Other requirements*	29	5	1457
Diatrizoate Meglumine—*Labeling, USP Reference standards, Other requirements*	30	3	832
Diatrizoate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1868

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Dibucaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Dicyclomine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1458
Diethylstilbestrol—*Labeling, USP Reference standards, Other requirements*	29	5	1463
Diethylstilbestrol Diphosphate Tablets (entire submission)	30	4	1187
Dihydroergotamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	6	1870
Dimenhydrinate—*Labeling, Other requirements*	29	5	1466
Dimercaprol—*Labeling, Other requirements*	29	5	1466
Diphenhydramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1466
Dipyridamole—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dobutamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1467
Dolasetron Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1468
Dopamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1469
Doxapram Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1874
Doxycycline Hyclate—*Content of ethanol*	30	3	836
Droperidol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1875
Dyphylline—*Labeling, USP Reference standards, Other requirements*	29	5	1473
Edetate Calcium Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edetate Disodium—*Labeling, USP Reference standards, Other requirements*	29	5	1474
Edrophonium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1475
Emetine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1875
Ephedrine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	3	840
Epinephrine—*Labeling, USP Reference standards, Other requirements*	29	5	1476
Ergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1478
Ergotamine Tartrate—*Labeling, USP Reference standards, Other requirements*	29	6	1884
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Fluphenazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1888
Flurandrenolide Lotion—*Title*	30	2	489
Flurandrenolide Topical Emulsion (entire submission)	30	2	489
†Fluvastatin Sodium—*USP Reference standards, Chromatographic purity*	31	1	43
†Fluvastatin Capsules—*USP Reference standards, Chromatographic purity*	31	1	47
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Gabapentin (entire submission)	29	1	72
Gadodiamide—*Labeling, Other requirements*	29	6	1889
Gadoteridol—*Labeling, USP Reference standards*	29	6	1890
Gallamine Triethiodide—*Labeling, USP Reference standards, Other requirements*	29	5	1503
Ganciclovir—*Labeling, USP Reference standards, Other requirements*	29	6	1890
Glucagon—*Labeling, USP Reference standards, Other requirements*	30	5	1625
Glycerin—*Labeling, Other requirements*	29	6	1895
Glycopyrrolate—*Labeling, USP Reference standards, Other requirements*	29	5	1503
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Hydrocortisone—*Labeling, USP Reference standards, Other requirements*	29	5	1506
Hydrocortisone Lotion—*Title*	30	2	505
Hydrocortisone Topical Emulsion (entire submission)	30	2	506
Hydrocortisone Acetate Lotion—*Title*	30	2	504
Hydrocortisone Acetate Ointment—*Assay*	30	2	504
Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	504
Hydromorphone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	4	1254
Hydroxyprogesterone Caproate—*Labeling, Other requirements*	29	5	1506
Hydroxyzine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1902
Hyoscyamine Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Imipramine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1904
Inamrinone—*Labeling, USP Reference standards, Other requirements*	29	5	1507
Indigotindisulfonate Sodium—*Labeling, USP Reference standards, Other requirements*	29	6	1905
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Insulin Human—*Labeling, Other requirements*	29	6	1906
Inulin—*Labeling, USP Reference standards, Other requirements*	29	6	1906
Iodipamide—*Labeling, USP Reference standards, Other requirements*	29	6	1907
Iodixanol—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1908
Iohexol—*Labeling, USP Reference standards, Other requirements*	29	6	1908
Iopamidol—*Labeling, USP Reference standards, Other requirements*	29	6	1909
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Isoproterenol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1509
Ketamine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1913
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Labetalol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1916
Leuprolide Acetate Injection (new)—*Preview*	25	5	8722
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Lidocaine Hydrochloride and Epinephrine Injection—*Assay for lidocaine hydrochloride, Assay for epinephrine*	30	4	1257
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Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (entire submission)	26	4	1050
Magnesium Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1921
Malathion Lotion—*Title*	30	2	513
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Mangafodipir Trisodium—*Labeling, Other requirements*	30	6	2014
Manganese Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1526
Manganese Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1922
Mannitol (entire submission)	27	5	3017
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Mebrofenin—*Labeling, USP Reference standards, Other requirements*	29	6	1923
Medroxyprogesterone Acetate—*Labeling, Other requirements*	29	5	1526
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Mepivacaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1533
Mesoridazine Besylate—*Labeling, USP Reference standards, Other requirements*	30	4	1262
Metaraminol Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1533
Methadone Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1929
Methocarbamol—*Labeling, USP Reference standards, Other requirements*	29	6	1930
Methohexital—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methotrimeprazine—*Labeling, USP Reference standards, Other requirements*	29	6	1931
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Methylbenzethonium Chloride Topical Powder—*Assay*	30	2	516
Methyldopate Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylene Blue—*Labeling, USP Reference standards, Other requirements*	29	5	1534
Methylergonovine Maleate—*Labeling, USP Reference standards, Other requirements*	29	5	1535
Methylphenidate Hydrochloride (new)—*Preview*	30	2	731
Methylprednisolone Acetate—*Labeling, Other requirements*	29	5	1535
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Morphine Sulfate—*Labeling, USP Reference standards, Other requirements*	30	5	1639
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Nandrolone Decanoate—*Labeling, Other requirements*	29	5	1539
Neomycin Sulfate and Flurandrenolide Lotion—*Title*	30	2	516
Neomycin Sulfate and Flurandrenolide Topical Emulsion (entire submission)	30	2	516
Neomycin Sulfate and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Lotion—*Title*	30	2	517
Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion (entire submission)	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	518
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment—*Assay for hydrocortisone acetate*	30	2	519

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Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment—*Assay for hydrocortisone acetate*	30	2	519
Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream—*Assay for hydrocortisone acetate*	30	2	520
Neostigmine Methylsulfate—*Labeling, Other requirements*	29	6	1936
Diluted Nitroglycerin—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Norepinephrine Bitartrate—*Labeling, USP Reference standards, Other requirements*	29	5	1547
Nystatin Lotion—*Title*	30	2	522
Nystatin Topical Emulsion (entire submission)	30	2	522
Ofloxacin—*Labeling, USP Reference standards, Other requirements*	30	4	1274
Ondansetron Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	29	6	1941
Orphenadrine Citrate—*Labeling, USP Reference standards, Other requirements*	30	2	523
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Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension—*Assay for hydrocortisone acetate*	30	2	528
Pentobarbital—*Labeling, USP Reference standards, Other requirements*	30	1	154
Pentobarbital Sodium—*Labeling, USP Reference standards, Other requirements*	30	1	157
Perphenazine—*Labeling, USP Reference standards, Other requirements*	29	6	1963
Phenobarbital—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phentolamine Mesylate—*Labeling, USP Reference standards, Other requirements*	29	5	1562
Phenylbutazone Injection—*USP Reference standards*	29	6	1964
Phenylephrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1964
Phenytoin Sodium—*Labeling, USP Reference standards, Other requirements*	30	6	2030
Physostigmine Salicylate—*Labeling, USP Reference standards, Other requirements*	29	6	1967
Potassium Chloride—*Labeling, USP Reference standards, Other requirements*	29	5	1562
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Prochlorperazine Edisylate—*Labeling, USP Reference standards, Other requirements*	29	5	1565
Progesterone—*Labeling, Other requirements*	29	5	1566
Promazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1566
Promethazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1567
Propoxycaine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	30	6	2032
Propranolol Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Propyliodone—*Labeling, Other requirements*	29	6	1976
Pyridostigmine Bromide—*Labeling, USP Reference standards, Other requirements*	29	6	1977
Quinidine Gluconate—*Labeling, USP Reference standards, Other requirements*	29	5	1568
Ranitidine Hydrochloride—*Labeling, USP Reference standards (USP Endotoxin RS), Other requirements*	30	6	2033
Ranitidine Oral Solution—*USP Reference standards, Identification, Chromatographic purity, Assay*	28	2	360
Reserpine—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Ritodrine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1570
Selenious Acid—*Labeling, USP Reference standards, Other requirements*	29	5	1571
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Sodium Thiosulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1579
Sufentanil Citrate—*Labeling, USP Reference standards, Other requirements*	29	6	1988
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Sulfamethoxazole—*Labeling, Other requirements*	29	6	1989
Terbutaline Sulfate—*Labeling, USP Reference standards, Other requirements*	29	5	1585
Terbutaline Sulfate Inhalation Aerosol (entire submission)	26	3	753
Terbutaline Sulfate Injection—*USP Reference standards, Identification, Assay*	26	3	756
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Theophylline—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiopental Sodium—*Labeling, USP Reference standards, Other requirements*	29	5	1586
Thiothixene Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993

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Triamcinolone Acetonide Topical Emulsion (entire submission)	30	2	538
Trifluoperazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1993
Triflupromazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	1994
Trimethobenzamide Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1589
Trimethoprim—*Labeling, Other requirements*	29	6	1995
Trimethoprim Sulfate—*Labeling, USP Reference standards, Other requirements*	29	6	1995
Tubocurarine Chloride—*Labeling, USP Reference standards, Other requirements*	29	6	1996
Urofollitropin (new) (entire submission)	28	6	1875
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Vasopressin—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Verapamil Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	5	1598
Xylazine—*Labeling, USP Reference standards, Other requirements*	29	6	2004
Xylazine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
Yohimbine Hydrochloride—*Labeling, USP Reference standards, Other requirements*	29	6	2005
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Fish Oil Rich in Omega-3 Acids Capsules (new) (entire submission)	29	4	1278
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⟨11⟩ USP Reference Standards			
USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS	30	6	2092
USP Fluoxetine Related Compound B Solution RS	30	4	1338
USP Methylphenidate Related Compound B RS	30	2	613
USP Methylphenidate Related Compound C RS	30	2	613
USP Methylphenidate Related Compound D RS	30	2	613
USP Methylphenidate Related Compound E RS	30	2	613
USP Methylphenidate Related Compound F RS	30	2	613
USP Methylphenidate Related Compound G RS	30	2	613
USP Methylphenidate Related Compound H RS	30	2	613
USP Paclitaxel Related Compound C RS	30	4	1338
USP Phenylephrine Bitartrate RS	30	3	998
USP Tazobactam Sodium RS	29	3	711

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⟨621⟩ Chromatography			
†*Chromatographic Reagents, Packings* (Enoxaparin Sodium Injection, IonPac AG11)	29	6	2023
†*Chromatographic Reagents, Packings* (Enoxaparin Sodium Injection, IonPac AS11)	29	6	2023
†*Chromatographic Reagents, Packings* (Enoxaparin Sodium, Dowex 1X8)	29	6	2023
†*Chromatographic Reagents, Packings* (Enoxaparin Sodium, Dowex 50WX2)	29	6	2023
Chromatographic Reagents, Phases (Docosahexaenoic Acid)	29	6	2023
⟨643⟩ Total Organic Carbon (entire submission)	30	5	1700
⟨701⟩ Disintegration—*Harmonization*	28	5	1575
⟨711⟩ Dissolution—*Harmonization*	28	6	1981
⟨776⟩ Optical Microscopy—*Harmonization*	28	2	606
⟨786⟩ Particle Size Distribution by Analytical Sieving—*Harmonization*	28	5	1581
⟨811⟩ Powder Fineness (entire submission)	28	2	611
⟨943⟩ X-Ray Diffraction—Solids (new) (entire submission)	28	3	905
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⟨1174⟩ Powder Flow (new)—*Harmonization*	28	2	618
⟨1198⟩ Standardized Imprint Codes for Solid Oral Dosage Forms (new)—*Preview*	28	1	152
⟨1225⟩ Validation of Compendial Methods—*Validation—Ruggedness*	30	4	1382
Dietary Supplements Chapters			
⟨2091⟩ Weight Variation of Nutritional Supplements (entire submission)	28	5	1548
Reagents, Indicators, and Solutions			
Air–Nitrous Oxide Certified Standard (added)	28	4	1233
4-Chlorophenol (added)	30	3	1045
Dioleoylglycerol (added)—*Preview*	26	6	1622
Monooleoylglycerol (added)—*Preview*	26	6	1622
Pentadecanoic Acid Methyl Ester (added)—*Preview*	26	6	1622
1,1,4,4-Tetraphenyl-1,3-butadiene (added)	26	6	1623
Trioleoylglycerol (added)—*Preview*	26	6	1623
Reference Tables			
Container Specifications			
Diethylstilbestrol Diphosphate Tablets	30	4	1404
Description and Relative Solubility			
Polydecene (added)	30	4	1405
Excipients			
Polydecene	30	4	1317
NF Monographs			
Adipic Acid—*Packaging and storage*	30	4	1322
Cellaburate—*Packaging and storage*	30	3	967
Microcrystalline Cellulose *(Harmonization)—Packaging and storage*	30	4	1435
Powdered Cellulose *(Harmonization)—Packaging and storage*	30	4	1438
Docosahexaenoic Acid (new)—*Preview*	26	6	1648
Docosahexaenoic Acid Capsules (new)—*Preview*	26	6	1651
Docosahexaenoic Acid Oil (new)—*Preview*	26	6	1652
Ethylparaben *(Harmonization)—Packaging and storage*	30	4	1444
Maltol—*Packaging and storage*	30	3	984

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* 31(1)–*PF* 31(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Medium-Chain Triglycerides—*Packaging and storage*	30	3	998
Methylparaben *(Harmonization)—Packaging and storage*	30	4	1446
Nitrogen—*Assay*	28	4	1219
Nitrogen 97 Percent—*Assay*	28	4	1220
Phenolsulfonphthalein—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94
Phenoxyethanol—*Labeling, USP Reference standards, Bacterial endotoxins*	31	1	94
Polydecene (entire submission)	30	4	1331
Polyethylene Glycol (entire submission)—*Preview*	29	4	1313
Propylparaben *(Harmonization)—Packaging and storage*	30	4	1448

†New cancellations in *PF* 31(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.

GENERAL CHAPTERS

General Information

BRIEFING

〈**1216**〉 **Tablet Friability,** *USP 28* page 2745 and page 3608 of the *Second Supplement.* The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the specifications provided in this general information chapter. The regional **Adoption Stage 6A** text was published in the *Second Supplement* to *USP 28–NF 23.* Revisions presented herein include the addition of a new opening paragraph to indicate that this chapter has now been harmonized and implemented by the United States Pharmacopeia, the European Pharmacopoeia, and the Japanese Pharmacopoeia. Other revisions clarify portions of the text. In the absence of any significant adverse comment, it is proposed to implement these revisions via the *Second Interim Revision Announcement* pertaining to *USP 29–NF 24,* with a delayed implementation date of **1 August 2006**.

(PDF: W. Paul) RTS—43195-1

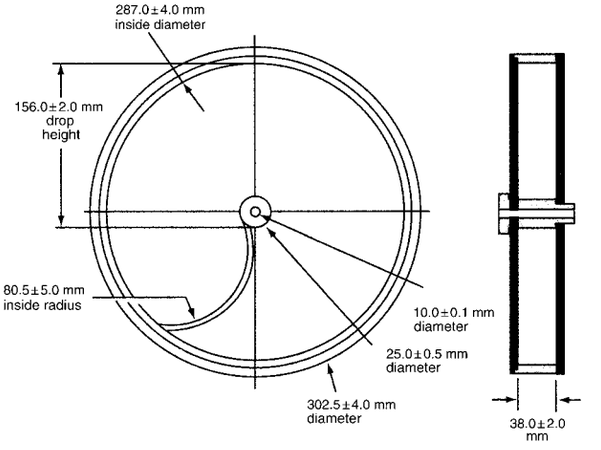
Change to read:

•This general information chapter has been harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. The harmonized texts of these three pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present *United States Pharmacopeia* general information chapter method. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.•2

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet ~~crushing strength~~ •breaking force.•2

Use a drum,* with an internal diameter between 283 and 291 mm and a depth between 36 and 40 mm, of transparent synthetic polymer with polished internal surfaces, and ~~not~~ ••2 subject to •minimum.•2 static build-up (see figure for a typical apparatus). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5 and 85.5 mm that extends from the middle of the drum to the outer wall.

•The outer diameter of the central ring is between 24.5 and 25.5 mm.•2 The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.



Tablet Friability Apparatus

For tablets with a unit ~~mass~~ •weight•2 equal to or less than 650 mg, take a sample of whole tablets corresponding •as near as possible•2 to 6.5 g. For tablets with a unit ~~mass~~ •weight•2 of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are ~~doubtful~~ •difficult to interpret•2

* The apparatus meeting these specifications is available from laboratory supply houses such as VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513, or from Erweka Instruments, Inc., 56 Quirk Road, Milford, CT 06460.

or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. A maximum ■mean■2S (*USP28*) weight loss ■from the three samples■2S (*USP28*) of not more than ■1.0%■2S (*USP28*) is considered acceptable for most products. ■■2S (*USP28*)

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the ~~bench top~~ •horizontal•2 and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. ■■2S (*USP28*) In the case of hygroscopic tablets, ■an appropriate■2S (*USP28*) humidity-controlled environment ■■2S (*USP28*) is required for testing.

■Drums with dual scooping projections, or an apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.■2S (*USP28*)

•(Official August 1, 2006)•2

Harmonization

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:

(DSN: L. Evans) 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.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

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.

Copyright—Copyright transfer documents will be sent to authors after manuscripts have been accepted for publication.

Contact Person—When submitting a manuscript, designate one author of the article as correspondent and include that author's full address, telephone number, fax number, and e-mail address.

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Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852

USP Advisory Panels on the USP Performance Test

L. Shargel, *Chair, Advisory Committee on Performance Tests (Injections),* and T. Foster, *Chair, Biopharmaceutics Expert Committee*

ABSTRACT USP's mission is to promote public health and benefit practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery. USP publishes the *United States Pharmacopeia (USP)* and *National Formulary (NF),* which contain monographs and associated information for more than 3,800 medicines, dietary supplements, and other health care products. Standards in a pharmacopeial monograph include introductory statements (definition, description, and packaging and storage statements), followed by a specification (tests, procedures, and acceptance criteria). A key test in the drug product monograph is the USP Performance test, which is a specific (not universal) test in ICH terminology (*1*).

INTRODUCTION

This and a following *Stimuli* article ("Critical Quality and Performance Parameters for Modified-Release Parenteral Dosage Forms") provide information about ongoing activities that are intended to improve and expand upon the USP Performance test. The activities are proceeding in Advisory Panels that were formed in connection with the Council of Experts Biopharmaceutics Expert Committee in the 2000–2005 cycle. With adjustments in membership, these Advisory Panels will continue in the current cycle (membership is shown in Appendix 1).

BACKGROUND

Following regulatory documentation of bioavailability (BA) and bioequivalence (BE), if required, and market access, if approved, the USP Performance test becomes the sole means of directly monitoring the ongoing performance of a dosage form or dietary supplement product that may be marketed perhaps for many years. For this reason, the work of the Advisory Panels and that of the Biopharmaceutics Expert Committee is especially important to the public health.

USP publishes monographs for both ingredients and products, including pharmaceutical dosage forms (drug products) and dietary supplement products. A key test in the product monograph for nonsolution dosage forms is the USP Performance test, which assesses release of the drug or dietary supplement in vitro. Under appropriate circumstances, the USP Performance test links to BA and BE studies, which are subject to regulatory review. Without this linkage, the USP Performance test should be viewed solely as a quality control test. For orally administered drug products, procedures and acceptance criteria for the USP Performance test appear in General Chapters ⟨701⟩ *Disintegration,* ⟨711⟩ *Dissolution,* and ⟨724⟩ *Drug Release*. Individual product monographs may then refer to these General Chapters with suitable Drug Release adjustments in the procedure to account for a specified dosage form or dietary supplement product.

In November 2002, USP formed an Ad Hoc Committee composed of members with expertise in pharmaceutical dosage forms, biopharmaceutics, and nomenclature, who worked with the Pharmaceutical Dosage Forms Expert Committee to develop a pharmaceutical dosage forms taxonomy scheme and related glossary. This taxonomy scheme and glossary were published as a *Stimuli* article in the September–October 2003 issue of *Pharmacopeial Forum* (*2*). The taxonomy scheme is tiered: The first grouping arranges dosage forms according to five routes of administration; the second grouping aligns them by dosage form type and physical properties (e.g., solid, semisolid, liquid, gas, or aerosol; and the third groups them according to the release pattern of the active pharmaceutic ingredient and performance characteristics of the dosage form. According to this 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].

Following the publication of this taxonomy *Stimuli* article, it became possible for USP to better consider dosage form specifications and to focus on improving and/or expanding the USP Performance test for dosage forms grouped by route of administration and other factors. This consideration began in the 2000–2005 cycle with creation of four Advisory Panels in connection with the USP Council of Experts Biopharmaceutics Experts Committee:

- Parenteral
- Inhalation/Aerosol

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- Topical/Dermal
- Mucosal.

Deliberations on the oral route of administration were reserved for the Biopharmaceutics Expert Committee itself. The current membership of each Panel and chair appear in the Appendix to this *Stimuli* article. According to USP's rules and procedures, the chair must be a member of the Biopharmaceutics Expert Committee.

DISCUSSSION

USP recognizes that the task of the Advisory Panels and of the Biopharmaceutics Expert Committee in improving and expanding on the USP Performance test for drug products by route of administration is not a simple one. Although this performance test, in both its public and private presentations, has been of considerable value in ensuring the quality and performance of dosage forms/products in the U.S. and other markets, the general approach requires continued careful scientific study, deliberation, and adjustment as needed (*3*). Further, it must be viewed in the context of national and international advances in regulatory control, not only in terms of development information in support of a regulatory filing (e.g., the product development report and quality-by-design approaches), but also in terms of post-approval change and ongoing adherence to current Good Manufacturing Practices (e.g., process analytical technology) even in the absence of change.

Even when the approach has been widely applied, as in the case of orally administered dosage forms, new advances and a stronger scientific understanding are possible (*4*). For other routes of administration, for which the number and types of dosage forms are rapidly evolving, the task of developing a valid specification to include a USP Performance test in applicable private or public approaches becomes even more daunting. Although the outcome of the deliberations of the Advisory Panels and Biopharmaceutics Expert Committee remains to be fully defined, USP envisions perhaps one or more General Chapters for each route of administration, just as there are now three General Chapters (cited above) for orally administered dosage forms (and, if applicable, this work may include dietary supplement products). Manufacturers submitting a Request for Revision (*5*) for either a new monograph or to update an existing monograph may then refer to these General Chapters in establishing a public standard for a particular dosage form/product and route of administration. Thus, the approach would follow the one that is now well-established for orally administered dosage forms.

USP ADVISORY PANEL ON INJECTABLE DOSAGE FORM PERFORMANCE

An accompanying *Stimuli* article has been prepared by the USP Advisory Panel on Parenteral/Injectable Dosage Form Performance,* which held its first meeting on 27 September 2004 at the time of USP's First Annual Scientific Meeting. This meeting included a track on regulatory and compendial goals in setting specifications for the performance of drug products. In this track, reports of the prior two workshops were summarized. The first was an AAPS-, FDA-, and USP-sponsored workshop report, ''Assuring Quality and Performance of Sustained- and Controlled-Release Parenterals'' (*6*), held in the Washington, DC, area. The second was held in Basel, Switzerland (*7*). At this initial meeting of the Advisory Panel in September 2004, key recommendations were to:

- Define essential product characteristics that are critical to product performance;
- Provide nomenclature for sustained- and controlled-release parenterals, including stents, nanosystems, liposomes, implants, etc., that is consistent with the tiered nomenclature structure proposed in the taxonomic scheme outlined in the *Pharmacopeial Forum Stimuli* article (*2*);
- Review preexisting information, including reports from the workshops on sustained- and controlled-release parenterals;
- Investigate apparatus, media, and calibrators for use in drug release studies in vitro;
- Investigate the linking of in vitro drug release studies to in vivo drug performance (i.e., BA).

The Advisory Panel envisioned continued research to substantiate the value and applicability of performance tests for the specified group of dosage forms with the goal of assisting regulatory and compendial authorities in understanding how to develop the needed procedures and acceptance criteria. In the current cycle, the Advisory Panel has prepared the following *Stimuli* article as a means of gaining public input to and assuring transparency about its deliberations. Through work of the Prescription/Nonprescription Stakeholder Forum, USP plans to form a Project Team that will monitor the work of the Biopharmaceutics Expert Committee and the four Advisory Panels to gain specific advice about the complex set of issues that will require consideration. This new Project Team will continue the deliberations of Project Teams 5 and 6 in the prior cycle.

SUMMARY

The USP Performance test is an important tool among the list of tests, procedures, and acceptance criteria that form the dosage form/product specification. USP has created Advisory Panels to study application of the USP Performance test to dosage forms grouped by four specified routes of ad-

* For membership list, see Appendix 1.

ministration. All Advisory Panels will work under the direction of the Biopharmaceutics Expert Committee. Consideration of issues for the USP Performance for a fifth route (oral) will be considered by the Biopharmaceutics Expert Committee itself. The following *Stimuli* article is one of several planned to ensure that USP maintains the highest scientific and public health approaches to compendial tests to assure the safety, quality, and efficacy of compendial articles.

APPENDIX 1: MEMBERSHIP OF THE 2005–2010 ADVISORY PANELS

Members of the USP Advisory Panel for Injectable Dosage Forms Performance are the following: Leon Shargel, Ph.D. (Chair); Jim Boylan, Ph.D. (Vice chair); Diane J. Burgess, Ph.D.; Brian Clark; Mary Jo Hampson-Carlin, B.S., M.B.A.; Pankaj Shah, Ph.D.; Mary Stickelmeyer, Ph.D.; David Young, Ph.D.; and Horacio Pappa, Ph.D. (USP Liaison).

The USP Advisory Panel for Gastro-Intestinal Dosage forms comprises the entire Biopharmaceutics Expert Committee, which includes the following members: Thomas S. Foster, Pharm.D. (Chair); Diane J. Burgess, Ph.D.; G. Bryan Crist, B.S.; Mario A. Gonzalez, Ph.D.; Vivian A. Gray, B.S.; Johannes Kraemer, Ph.D.; Lewis J. Leeson, Ph.D.; Alan F. Parr, Pharm.D., Ph.D.; James E. Polli, Ph.D.; Leon Shargel, Ph.D.; Eli Shefter, Ph.D.; William C. Simon, Ph.D.; Clarence T. Ueda, Pharm.D., Ph.D.; David Young, Pharm.D., Ph.D.; William E. Brown (USP Liaison); and Margareth R.C. Marques, Ph.D. (USP Liaison).

Members of the USP Advisory Panel for Topicals are the following: Clarence T. Ueda, Ph.D. (Co-chair); Vinod P. Shah, Ph.D. (Co-chair); Kris Derdzinski, Ph.D.; Gary Ewing, Ph.D.; Gordon Flynn, Ph.D.; Howard Maibach, Ph.D.; Steve Shaw, Ph.D.; Kailas Thakker, Ph.D.; Avi Yacobi, Ph.D.; and Margareth R.C. Marques, Ph.D. (USP Liaison).

Members of the USP Advisory Panel for Inhalation Products will be recruited because this Advisory Panel is currently in development.

Members of the USP Advisory Panel for Mucosal Products are the following: Eli Shefter, Ph.D. (Chair); Tom Foster, Pharm.D. (Chair, Biopharmaceutics Expert Committee); Lisbeth Ankersen; Bruce Aungst, Ph.D.; Stuart Bates; Sarath Chandar, M.B.A.; Munir Hussain, Ph.D.; Johannes Kraemer, Ph.D.; and William E. Brown (USP Liaison).

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Critical Quality and Performance Parameters for Modified-Release Parenteral Dosage Forms

Diane J. Burgess, *University of Connecticut;* Brian C. Clark, *AstraZeneca, Macclesfield, UK;* Mary Joan Hampson-Carlin, *Laureate Pharma;* and Pankaj Shah, *Bristol-Myers Squib*[*]

ABSTRACT This *Stimuli* article addresses the use of performance tests and the setting of specifications for controlled-release parenteral products. Although each product must be regarded on a case-by-case basis, a set of general guidelines may facilitate product development and marketing approval to ensure drug product safety and efficacy. Controlled-release parenterals encompass a range of products with commonalities and also unique properties. Therefore, different categories of specifications can be considered, including those that are standard among all products and those that are product specific. This article defines controlled-release parenterals and discusses factors that affect bioavailability from intramuscular (IM) and subcutaneous (SC) sites. A list describes the necessary critical quality parameters common to all controlled-release dosage forms as well as those that are specific to certain dosage forms or drug products. In addition, the *Stimuli* article attempts to categorize controlled-release parenteral dosage forms on the basis of specifications that are necessary for product development purposes and those that are necessary for quality control.

INTRODUCTION

In 2004 USP created Advisory Panels to address critical quality and performance parameters for injectable, oral, aerosol, topical, and mucosal products (*1*). The information generated by the Advisory Panels could lead to companion General Chapters in *USP–NF* to complement the existing General Chapters on the quality control of various drug products. Specifications for product performance may also be generated and would be included in individual monographs. This article is the result of the efforts of the USP Advisory Panel on Performance Tests—Injections. Panel members are listed at the end of the article.

CONTROLLED-RELEASE PARENTERAL DOSAGE FORMS

Controlled-release drug delivery systems are defined in *USP* as: "dosage forms that allow for the uniform release or targeted delivery of drugs to the body." These dosage forms are used to improve therapeutic responses by providing blood levels that are more consistent and stable compared to those of multiple doses of immediate-release dosage forms. Controlled-release parenteral products can result in a reduction in adverse reactions due to less fluctuation in plasma or tissue drug concentrations, and for targeted-delivery products high systemic levels are avoided. As a consequence of targeted and controlled release, patient compliance may be improved due to lower dosing frequencies and simpler dosing regimes. Controlled-release parenteral drug delivery systems include the following: suspensions, liposomes, microspheres, gels, and implants. Tiny microspheres and larger implantable devices, such as stents, can be used to achieve extended release during periods ranging from months to years. Suspensions, liposomes, and gels may not achieve quite as long a duration of action; however they can be localized at the site in vivo, and liposomes may achieve targeted delivery both by passive and active means following intravenous administration. These delivery systems are becoming increasingly utilized by the pharmaceutical industry to deliver drugs for treatment or prevention of a variety of diseases.

Not all drugs are candidates for controlled parenteral delivery. The drug should be potent with known toxicity and pharmacokinetic profiles. The drug should not have a narrow therapeutic index. A controlled-release parenteral dosage form usually is selected when there are problems associated with oral delivery (e.g., gastric irritation, first-pass effects, or poor absorption) and a need for extended release or targeted delivery (e.g., rapid clearance). Both systemic and localized delivery can be achieved. In addition, the drug must be compatible with the manufacturing process, which may be fairly harsh for some of these products. Examples of disease applications for controlled-release parenteral delivery include the following: fertility treatments, hormone therapy, protein therapy, treatment of infections (e.g., antibiotics and antifungals), cancer therapy, orthopedic surgery, post-operative pain, chronic pain, vaccination/immunization, central nervous system disorders (e.g., Alzheimer's and schizophrenia), anti-seizure applications, and immunosuppression.

Routes of administration for controlled-release parenterals include intravenous (IV), intra-articular (IA), subcutaneous (SC), and intramuscular (IM). The IV and IA routes by their nature result in 100% bioavailability. However, drug absorption from the SC and IM sites can be erratic and variable as a consequence of differences in physiologi-

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cal parameters, such as drainage and blood flow that result from muscle activity and inflammation, as well as physiological reactions to injection trauma. The SC route shows poor blood flow and drainage compared to the IM route. The muscle site and the injection technique may influence absorption. Different absorption profiles result from intra- and intermuscular injections (within and between the muscle fibrils, respectively).

After SC and IM administration, absorption of drugs encapsulated in carrier systems depends on release of the drug from the carrier, absorption of the free drug, and, in some cases, absorption of the carrier. Following release, the drug will behave as if administered in conventional formulations, and general biopharmaceutical principles will apply. However, if the carrier is absorbed from the injection site as an intact unit, the drug will follow the kinetics and biodistribution of the carrier. This may occur for small liposomes and other particulates with particle size of approximately 100 nm or less. Such particulates are taken up by the lymphatic capillaries, and from there they reach the general circulation. Oussoren et al. provide a comprehensive treatment of biopharmaceutical aspects of controlled-release parenterals (*2*).

DEFINITION OF SPECIFICATIONS

ICH defines a specification as a list of tests, procedures, and acceptance criteria for a substance, an excipient, a product, a package, or other component used in manufacturing. According to the AAPS workshop report, "Assuring Quality and Performance of Sustained- and Controlled-Release Parenterals," cosponsored by FDA and USP (*3*), it is important to identify critical parameters during the development process. Critical parameters include extensive physical/chemical characterization and an understanding of the impact of formulation variables on physical/chemical factors. For example, drug stability and drug release are important in vitro parameters for which specifications must be set because these influence in vivo performance. In vivo it is important to understand pharmacokinetics, safety, and efficacy. There are different categories of quality and performance attributes for controlled-release parenteral dosage forms, including the following: 1) those that are standard for parenteral systems regardless of the drug or the delivery system; 2) those that are specific to the drug; 3) those that are specific to the drug delivery system; and 4) those that are specific to the drug product. Listed immediately below are specifications in categories *1* and *2*. Those for categories *3* and *4* are listed separately for each dosage form. In addition, the specifications are further categorized as follows: general (denoted as *G*); research and development (denoted as *R&D*); and stability (denoted as *S*).

General tests are those performed throughout the product life cycle to support formulation development, clinical supply, and quality control of commercial supplies. *R&D* tests are those carried out during the R&D phase only in order to characterize the product. Stability tests are those done in addition to the general tests as part of a study to investigate degradation pathways, confirm storage conditions, and assess the effects of changes in the manufacturing process. Specifications should apply throughout the product shelf life, and therefore methods should be stability-indicating when appropriate (e.g., potency, impurities, and drug release).

Specifications Common to All Parenteral Controlled-Release Delivery Systems

1. Standard specifications for parenteral systems
   - Appearance *(G)*
   - Identity *(G)*
   - Assay *(G)*
   - pH (not for a solid or nonaqueous dosage form) *(G)*
   - Osmolarity (not for a solid or nonaqueous dosage form) *(G)*
   - Water content (for solid or nonaqueous dosage form) *(G)*
   - Residual solvent (test needed if solvents are used in the manufacturing process) *(G)*
   - Sterility *(G)*
   - Particulates (other than the delivery system itself, if a dispersed system product such as liposomes) *(G)*
   - Bacterial endotoxin or pyrogen test *(G)*
2. Drug-specific
   - Drug potency *(G)*
   - Drug-related substances *(G)*
   - Dose uniformity in the suspending agent *(G)*
   - Drug stability *(S)*

Liposomes

Formulations may contain an active pharmaceutical ingredient encapsulated in a liposome (either within the lipid bilayer or dissolved in the interior aqueous space of the liposome). Administration may be by IV, SC, or IM injection. Liposomes may be supplied as a suspension or in the dry form, with a suspending medium for constitution immediately prior to use. In the latter case, a separate specification is needed for the method of suspension and the suspending medium (one must consider pH, osmolarity, and viscosity), and a performance test is required to ensure proper reconstitution.

3. Drug delivery system–specific
   - Particle size *(G)*
   - Percent free vs. percent encapsulated *(G)*
   - pH *(G)*
   - Drug release *(G)*
   - Protein binding (including lipoprotein; determine degree of binding and nature of binding proteins) *(R&D)*
4. Product-specific
   - Lipid assay(s) *(G)*
   - Fatty acid composition *(G)*
   - Positional specificity (acyl side chains) *(R&D)*
   - Degree of fatty acid unsaturation *(R&D)*

- Phosphatidylglycerol/phosphatidyl serine (lecithin preparations) *(R)*
- Lamellarity *(R&D)*
- Peroxidation measure *(G)*
- % Lyso lipid *(G)*
- Zeta potential *(R&D)* and *(S)*
- Phase transition *(R&D)*
- Tissue reaction (IM and SC) *(R&D)*

Polymeric Microspheres and Nanoparticles

These formulations contain an active pharmaceutical ingredient entrapped in a polymeric matrix or encapsulated within a polymer wall and are defined as nanoparticles or microspheres, depending on the particle size. Administration may be IV (nanoparticles only), SC, or IM injection. Such dosage forms may be supplied as a suspension (this is unusual for microspheres) or in the dry form with a suspending medium for constitution immediately prior to use. In the latter case, one needs a separate specification for the suspending medium (covering pH, osmolarity, viscosity, and a performance test to ensure adequate suspension).

3. Drug delivery system–specific
   - Particle size and particle-size distribution, *(G)*
   - Porosity/surface area *(R&D)*
   - Percent free vs. percent encapsulated (for a suspension) *(G)*
   - pH (for an aqueous suspension) *(G)*
   - Osmolarity (for an aqueous suspension) *(G)*
   - Drug release *(G)*
   - Burst release *(G)*
   - Redispersibility *(G)*
   - Concentration and volume or weight *(G)*
   - Deliverable dose *(G)*
   - Syringability *(G)*
   - Core load (percent entrapped active) *(G)*
4. Product-specific:
   - Polymer molecular weight and polydispersity *(R&D)* and *(S)*
   - Copolymer ratio *(R&D)*
   - Glass transition point *(R&D)*
   - Morphology (surface and cross section) *(R&D)*
   - Tissue reaction *(R&D)*

Stents

Drug-eluting stents have a polymeric coating with entrapped active pharmaceutical ingredient on the surface of the metal stent. Drug is administered directly to the site of potential restenosis.

3. Drug delivery system–specific
   - Drug release test *(G)*
   - Burst release *(G)*
   - Coating thickness(es) *(G)*
   - Coating robustness and susceptibility to cracking on expansion *(R)*
   - Free drug vs. encapsulated drug *(G)*
4. Product-specific
   - Morphology (surface and cross section) *(R&D)*
   - Polymer molecular weight and polydispersity *(R&D)* and *(S)*
   - Copolymer ratio *(R&D)*
   - Glass transition point *(R&D)*
   - Coating adhesion to stent surface *(R&D)*
   - Tissue reaction *(R&D)*

Emulsions

Oil-in-water or water-in-oil emulsions typically entrap the active pharmaceutical ingredient within the dispersed phase. Administration may be by IV, SC, or IM injection. Emulsions also are used for parenteral nutrition (IV).

3. Drug delivery system–specific
   - Particle size and size distribution *(G)*
   - Percent free vs. encapsulated *(G)*
   - pH *(G)*
   - Free fatty acid *(G)*
   - Emulsifying agent *(G)*
   - Drug release rate (for a controlled-release formulation) *(G)*
   - Burst release (for a controlled-release formulation) *(G)*
4. Product-specific
   - Lipid assay(s) *(G)*
   - Zeta potential *(R&D)* and *(S)*

Suspensions

Although nanoparticles, microspheres, and liposomes are suspensions, the latter category is limited here to formulations in which an insoluble active substance is suspended in a suitable (usually aqueous) medium incorporating suspending agents, viscosity modifiers, surfactants, etc., as appropriate to avoid agglomeration and ensure suspendability of the drug. Suspensions usually are administered by IM or SC injection, although nanosuspensions may be suitable for IV administration.

3. Drug delivery system–specific
   - Particle size and size distribution *(G)*
   - Particle morphology, profile, and surface area *(G)*
   - Percent in solution vs. percent in solid form *(G)*
   - Syringability *(G)*
   - Viscosity *(G)*
   - Suspendability *(G)*
4. Product-specific
   - Crystallinity *(R&D)* and *(S)*
   - Polymorphs *(R&D)* and *(S)*
   - Tissue reaction *(R&D)* and *(S)*

Resuspendability tests (for powders, microspheres, or liposomes supplied in dry form for resuspension immediately prior to administration) involve the following:

4. Product-specific
   - Resuspendability *(G)*
   - Syringability *(G)*
   - Deliverable dose *(G)*

- Burst release *(G)*
- Particle-size distribution *(G)*

5. Suspending medium
   - pH *(G)*
   - Osmolarity *(G)*
   - Viscosity *(G)*
   - Particulate matter *(G)*
   - Color/clarity of solution *(G)*
   - Turbidity *(G)*

Monolithic Depot

A monolithic depot is a polymer-based, sustained-release formulation in which the active pharmaceutical ingredient may be dispersed (as discrete particles) in a polymer matrix or dissolved (as an ionic drug–polymer conjugate), presented as an implantable rod (or other appropriate shape) for IM or SC injection.

3. Drug delivery system–specific
   - Drug release *(G)*
   - Burst release *(G)*
   - Percent free vs. percent encapsulated active *(G)*
4. Product-specific
   - Solvent content *(G)*
   - Morphology (surface and cross section) *(R)*
   - Polymer molecular weight and polydispersity *(S)*
   - Copolymer ratio *(R&D)*
   - Glass transition point *(R&D)*

Oily Depot

An oily depot is an oil-based sustained-release formulation normally used for the delivery of water-insoluble pharmaceutical active ingredients that may include organic solvents as solubility/viscosity modifiers, presented as a clear solution for IM or SC injection.

3. Drug delivery system–specific
   - Drug release rate (for a controlled-release formulation) *(G)*
   - Burst release (for a controlled-release formulation) *(G)*
4. Product-specific
   Solvent content *(G)*
   Oil content *(G)*

Osmotic Pump Implant

Osmotic pump implants involve a formulation of pharmaceutical active ingredient in a core surrounded by semipermeable membrane that has a microdrill-produced orifice in order to release the active material at a constant rate. Within the body, fluid enters the core through the membrane and dissolves the active material. The osmotic pressure generated in the core induces release of the drug in solution at a slow but constant rate. The pump may consist of two compartments separated by a semipermeable membrane. In the latter case, one compartment contains an osmotic agent in solution form and the other, which has the outlet orifice, contains the active pharmaceutical agent.

3. Drug delivery system–specific
   - Drug release rate *(G)*
   - Semipermeable membrane thickness *(G)*
   - Active content *(G)*
   - Osmotic agent content *(R)*
   - Orifice diameter *(G)*
4. Product-specific
   - pH if the product contains a solution or suspension *(G)*
   - Osmolarity *(G)*

CONCLUSIONS

The USP Advisory Panel on Performance Tests—Injections is interested in receiving feedback on this *Stimuli* article to help in developing companion General Chapters in *USP–NF*, as well as specifications for product performance to be included in individual chapters. To this end, please send comments to Horacio Pappa, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, tel. 301.816.8319, e-mail hp@usp.org. It should be noted that validated methods and acceptance criteria for each of the tests listed here would have to be developed to support a regulatory application, unless a compendial approach is available.

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Compendial Calculations: Improving Calculations in *USP–NF*

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ABSTRACT The objective of this article is to propose a standardized format for calculations and a new approach for presenting calculation equations in *USP* General Chapters rather than in specific monographs. Analysts recognize that the equations that can be used for an analytical procedure are all fundamentally derived from a universal calculation. The format presented in this article is one approach to achieve the end result of a standardized format. The proposal, if adopted, will simplify the USP process by removing redundancies, conserving space, and minimizing the ambiguity that is encountered in the current calculation models, which often present a challenging task in analytical laboratories. For clarity and effectiveness, the proposed standardized approach for calculations is based on the use of units of measure. Several examples of calculations used in common analytical methods are presented to support the proposed format.

BACKGROUND

There are different ways to present calculation formulas for analytical methods. In comparing USP and industry practices, the PhRMA Compendial Liaison Team (CLT) found a significant gap in the level of detail between the two calculation formats used. The proposal in this *Stimuli* article attempts to bridge the gap and find an appropriate standardized format suitable for use both in *USP* and in pharmaceutical laboratories.

Chemists, technicians, and a variety of support personnel in laboratories around the world follow *USP* to ensure the consistent analysis of pharmaceutical substances and products. Although the calculation formulas in *USP* are common to the pharmaceutical industry, they are also complex and inconsistent throughout the compendium. Thus, personnel new to the industry and new to the laboratory face a steep learning curve and require a considerable amount of training in compendial matters, including calculations.

Consistent with the USP initiative to improve the compendium, this *Stimuli* article is published to solicit input via *Pharmacopeial Forum* for further development and discussion. PhRMA CLT feels that there is great merit in having more detailed formulas for calculations and in correcting the present deficiencies in three areas: inconsistency, redundancy, and ambiguity. To this end, we propose a new system for improving calculation instructions.

CURRENT STATUS

The current USP system for providing calculations is not optimal. Some monograph procedures and General Chapters provide information about calculations, but others do not. At the same time, common calculations, such as HPLC assay results, are repeated throughout the compendium. These calculations have been reduced to their absolute minimum to save space and keep *USP* to a functional size. Unfortunately, this format challenges a scientist's ability to understand and modify the calculations where allowable revisions have been made. For example, modifying an HPLC dilution sequence can affect the dilution factor used in the calculation, but many compendial calculations have incorporated the sample dilution factor into a calculation constant. Furthermore, combined calculation constants do not address units of measure or the source of special conversion factors (e.g., molecular weight conversions). This contributes to confusion and often leads to errors in the interpretation of the formulas, which can cause delays in laboratory reports, reviews, and investigations. It even affects personnel at USP because they are often contacted to clarify the requirements. Also, with each republication of the calculation in individual monographs, there is a potential for error.

On the other hand, the pharmaceutical industry attempts to apply "fool-proof" detailed calculations that cover every possible variable for each individual test. This approach is valuable so scientists worldwide can perform the same calculation in the same manner, without question or confusion. Unfortunately, these calculations have become so specialized that they are monograph and method specific. Therefore, they may not be appropriate for public standards, such as those in *USP*, because of the significant space that would be required to incorporate them into monographs.

RECOMMENDATION

The core of this proposal is to utilize the current compendial systems to provide a new means of referencing compendial calculation information. This approach has several

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benefits: It limits the overall impact on *USP;* it allows *USP* to incorporate changes in a shorter time frame; and it does not require industry to adopt dramatic changes.

Three areas were evaluated to establish the proposal.

- Format: The approach needs to be appropriate for multiple applications in order to reduce redundancies while providing sufficient information for laboratory personnel to accurately generate results.
- Application: PhRMA CLT evaluated several possible ways to incorporate calculation improvements into *USP:* creating a new section in the General Notices; improving the current General Chapters; adding a new General Chapter specifically devoted to compendial calculations; and developing the calculations within individual monographs.
- Growth: The proposal needs to be able to evolve with *USP.* As new monographs are proposed, what is the best way to evaluate and incorporate the changes without consuming significant resources?

With the addition of units of measure and information about correction factors, the current *USP* format will become more user-friendly for existing calculations with great benefit to the pharmaceutical industry, as well as other *USP* subscribers.

After evaluating the different ways to incorporate compendial calculations, we focused on updating General Chapters. Several disadvantages were apparent in the alternative approaches. Creating a new section in the General Notices or adding a new General Chapter devoted to calculation formulas would require significant revisions to every section of *USP* (General Notices, Monographs, and General Chapters). Revising the calculations in current monographs would require significant space in each monograph and continue with a system that contains redundancies. Because the purpose of General Chapters is to eliminate redundancies within the monographs, we decided to apply a system that exists but is not being applied to its full extent.

Modifications to General Chapters can be performed in a more efficient manner than updating individual monographs (current system). Therefore, developing General Chapters will allow a smoother transition with future updates.

PROPOSAL FOR CALCULATIONS

To improve the current *USP* practice for applying calculations, PhRMA CLT proposes to add common calculations to the General Chapters (Attachment 1). As appropriate, calculations can be replaced in individual monographs with references to the General Chapters. This would mean that only monograph-specific calculations would remain outside of the General Chapters (e.g., Povidone, K-value). Monograph methods would then reference the General Chapters, a specific formula reference (if required), and method-specific requirements (e.g., correction factors). Attachment 2 demonstrates how this new system would appear in a monograph.

IMPLEMENTATION

We recommend a three-step plan for implementation. First, the General Chapters need to be updated with the necessary information and formulas. Second, the compendial submission guidelines should be updated to the new calculation system, with a request for public submissions to revise the current monographs. Finally, the remaining monographs should be updated as needed.

CONCLUSION

By including calculation formulas in the General Chapters, USP can resolve inconsistencies and ambiguities that currently exist with compendial calculations. Additionally, USP can remove redundancies due to repeated printing of similar calculations in the individual monographs (e.g., HPLC calculations) and reduce the potential for error in the calculations published in the monographs. This will benefit all groups involved by reducing the size of the monographs and providing more user-friendly calculations that are adaptable (e.g., to account for user-specific dilutions, formula weight corrections, units of measure, etc.) while also providing critical information that is not currently available within *USP.*

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ATTACHMENT 1

Common Calculations

(NOTE: *Examples are included for the benefit of reviewers and are not intended for inclusion in* USP.)

- **Volumetric Solutions** (VS)

  Standardizing against Another VS (Formula 1):
  Calculation
  Normality of VS = N $\times$ V/V_U
  where
  N = Normality of the standardized VS (N)
  V = Volume of the standardized VS (mL)
  V_U = Volume of the unstandardized VS (mL)

  Example:
  30.0 mL of 0.1025 N silver nitrate VS is used to standardize ~0.1 N ammonium thiocyanate VS.

Experimental: 30.47 mL of ~0.1 N ammonium thiocyanate VS was used to titrate 30.0 mL of 0.1025 N silver nitrate VS.

0.1025 N × 30.0 mL/30.47 mL = 0.1009 N NH_4SCN VS

- **Volumetric Solutions (VS)**

Standardizing against a Primary Standard (Formula 2)
Calculation:
Normality of VS = N × W_S × $P_S/(V_U \times F)$
where
N = Theoretical normality
W_S = Weight of the primary standard (mg)
P_S = Purity of the primary standard (decimal)
V_U = Volume of the unstandardized VS (mL)
F = Conversion factor (mg primary standard/mL of VS as the theoretical normality)

Example:
~1 N hydrochloric acid VS standardized against 5 g tromethamine.

Experimental: 39.82 mL of ~1 N HCl was used to titrate 5.0005 g of tromethamine (99.98% pure).

121.14 mg of tromethamine is equivalent to 1 mL of 1 N hydrochloric acid.

1 N × 5000.5 mg × 0.9998 / (39.82 mL × 121.14 mg/mL) = 1.036 N HCl VS

- **Alcoholometric Table**

Extrapolation
Calculation:
Extrapolated Value = R_{U1} − [(R_{T1} − S) × (R_{U1} − R_{U2})/(R_{T1} − R_{T2})]
where
R_{T1} = Upper value of the test range
R_{T2} = Lower value of the test range
R_{U1} = Upper value of the unknown range
R_{U2} = Lower value of the unknown range
S = Experimental value

Example:
Specific Gravity (SG) for Alcohol determined at 25° converted to 15.56°

Experimental:
Sample SG = 0.7893 at 25°.

From the Alcoholometric table select the 25° and corresponding 15.56° range for your result:

25° (test range)	15.56° (unknown range)
0.7921	0.7986
0.7871	0.7936

$R_{T1} - R_{T2}$ = 0.7921– 0.7871 = 0.0050
$R_{U1} - R_{U2}$ = 0.7986 – 0.7936 = 0.0050
0.7986 – [(0.7921 – 0.7893) × 0.0050/0.0050] = 0.7958 SG at 15.56°

- **⟨281⟩ Residue on Ignition (ROI)**

Percent Residue on Ignition
Calculation:

$$\%\text{ROI} = \frac{(W_I - W_D)}{W_U} \times 100\%$$

where
W_U = Sample weight (g)
W_D = Crucible weight (g)
W_I = Weight of the ignited crucible and residue (g)

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

Experimental: 1.0293 g of sample was weighed into a 35.4688-g crucible.

The ignited sample and crucible weight was determined to be 35.4699 g.

$$\frac{(35.4699\ g - 35.4688\ g) \times 100\%}{1.0293\ \text{g}} = 0.1\%\text{ROI}$$

- **⟨541⟩ Titrimetry**

Direct titration (Formula 1)
Calculation:

$$\%\text{Assay} = \frac{(V_U - V_B) \times \text{N} \times F \times 100\%}{\text{N}_1 \times W \times (1 - A)}$$

where
V_U = Sample titration volume (mL)
V_B = Blank titration volume (mL)
N = Actual normality of the titrant (N)

F = Conversion factor (mg sample/mL of titrant as the theoretical normality)
N_T = Theoretical normality of the titrant (N)
W = Sample weight (mg)
A = Assay correction (decimal) [Loss on drying, Water, or Loss on ignition]

Example:
Dissolve about 200 mg of Sample, accurately weighed, in 10 mL of water and add 3 drops of indicator TS. Titrate with 0.1 N titrant VS to a pink endpoint. Each mL of 0.1 N titrant is equivalent to 5.844 mg of Sample (99.0% to 100.5% of Sample, calculated on the dried basis).

Experimental: 200.4 mg of Sample (0.1% LOD) was titrated with 34.25 mL of 0.1002 N titrant VS. The blank consumed 0.01 mL of 0.1002 N titrant VS.

$$\frac{(34.25\ \text{mL} - 0.01\ \text{mL}) \times 0.1002\ \text{N} \times 5.844\ \text{mg/mL} \times 100\%}{0.1\ \text{N} \times 200.4\ \text{mg} \times (1 - 0.001)} = 100.1\%\ \text{Assay}$$

- **⟨541⟩ Titrimetry**

Residual titration (Formula 2)
Note: This type of titration is identified by the addition of a primary VS to the test solution before the titration.
Calculation:

$$\%\text{Assay} = \frac{(V_B - V_U) \times \text{N} \times F \times 100\%}{N_T \times W \times (1 - A)}$$

V_B = Blank titration volume (mL)
V_U = Sample titration volume (mL)
N = Actual normality of the titrant (N)
F = Conversion factor (mg sample/mL of primary VS as the theoretical normality)
N_T = Theoretical normality of the titrant (N)
W = Sample weight (mg)
A = Assay correction (decimal) [Loss on Drying, Water, or Loss on Ignition]

Example:
Dissolve about 400 mg of Sample, accurately weighed, in 15 mL of water. Add 40.0 mL of 0.1 N primary VS. Add indicator TS, and titrate the excess with 0.1 N titrant VS. Perform a blank determination. Each mL of 0.1 N primary VS is equivalent to 18.17 mg of Sample (98.0% to 102.0% of Sample, calculated on the dried basis).

Experimental: 400.4 mg of Sample (0.1% LOD) was titrated with 18.01 mL of 0.1002 N titrant VS (40.0 mL of 0.0996 N primary VS was used in the procedure). The blank consumed 39.82 mL of 0.1002 N titrant VS.

$$\frac{(39.82\ \text{mL} - 18.01\ \text{mL}) \times 0.1002\ \text{N} \times 18.17\ \text{mg/mL} \times 100\%}{0.1\ \text{N} \times 400.4\ \text{mg} \times (1 - 0.001)} = 99.3\%\ \text{Assay}$$

- **⟨621⟩ Chromatography**

Calculations from a standard (Formula 1)

Calculation:

$$\textbf{Weight Result (mg)} = F \times C_S \times D \times (r_U / r_S)$$

or

$$\textbf{\%Result} = F \times (C_S / C_U) \times (r_U / r_S) \times 100\%$$

where
F = Correction factor equals 1 unless specified in the individual monograph
C_S = Concentration of standard solution (mg/mL) [Corrected for purity]
C_U = Concentration of test solution (mg/mL) [Corrected for Loss on Drying, Water, Loss on Ignition, Residual Solvents, etc. (as needed)]
D = Dilution for the test solution (mL)
r_U = Peak response(s) (area, height, etc.) or internal standard ratio (peak response of the analyte/peak response from the internal standard) obtained from the test solution

r_S = Peak response(s) (area, height, etc) or internal standard ratio (peak response of the analyte/peak response from the internal standard) obtained from the standard solution
Note: Correct peak responses for the blank injection as needed.

Example:
Mannitol, *NF—Assay* (96.0% to 101.5%, calculated on the dried basis).

Experimental:
Standard—120.4 mg USP Mannitol RS (100%) diluted to 25.0 mL. Assay—245.0 mg of Mannitol (0.1% LOD) diluted to 10.0 mL, further diluted 2.0 mL to 10.0 mL.
Peak Area (assay preparation)—79,221
Peak Area (standard preparation)—80,543
D = 10.0 mL × (10.0 mL/2.0 mL) = 50.0 mL
1 × 4.816 mg/mL × 50.0 mL × (79,221/80,543) = 236.8 mg

or

1 × (4.816 mg/mL/4.8951 mg/mL) × (79,221/80,543) × 100% = 96.8% Assay

• **⟨621⟩ Chromatography**

Calculations from a standard—Dosage Form (Formula 2)
Calculation:

$$\textbf{Weight Result (mg/unit)} = F \times (C_S / C_U) \times (r_U / r_S)$$

or

$$\textbf{\%Label Claim} = F \times (C_S / C_U) \times (r_U / r_S) \times (100\%/L)$$

where
F = Correction factor equals 1 unless specified in the monograph.
C_S = Concentration of standard solution (mg/mL) [Corrected for purity]
C_U = Concentration for the test solution (unit/mL) [Where unit = Tablet, Volume, Vial, etc.]
L = Label claim (mg/dosage form)
r_U = Peak response(s) (area, height, etc.) or internal standard ratio (peak response of the analyte/peak response from the internal standard) obtained from the test solution
r_S = Peak response(s) (area, height, etc.) or internal standard ratio (peak response of the analyte/peak response from the internal standard) obtained from the standard solution
Note: Correct peak responses for the blank injection as needed.

Example:
Active Tablets—Assay (90.0% to 110.0% of the labeled amount).

Experimental:
Standard—30.4 mg USP Alternative Active RS (99.5%) diluted to 100.0 mL.
Assay—20 tablets (3 mg/tablet) diluted to 200.0 mL.
Peak Area (assay preparation)—65,459
Peak Area (standard preparation)—68,534
Standard correction factor (F)—1.1

$$\frac{1.1 \times (0.304\ \text{mg/mL} \times 0.995) \times 60{,}746}{0.1\ \text{tablet/mL} \times 68{,}534} = 2.95\ \text{mg/tablet}$$

or

$$\frac{1.1 \times 0.304\ \text{mg/mL} \times 0.995 \times 60{,}746 \times 100\%}{0.1\ \text{tablet/mL} \times 68{,}534 \times 3\ \text{mg/tablet}} = 98.3\%\ \text{label claim}$$

• **⟨621⟩ Chromatography**

Area normalization (Formula 3)
Calculation:

$$\textbf{\%Impurities or \%Assay} = F \times (r_i / r_t) \times 100\%$$

where
F = Correction factor equals 1 unless specified in the monograph.
r_i = Individual peak response (area, height, etc.) obtained from the test solution
r_t = Sum of relevant peak responses (area, height, etc.) obtained from the test solution
Note: Correct peak responses for the blank as needed.

Example:
Inject a volume (about 20 µL) of the Test preparation into the chromatograph, record the chromatograms, and measure the peak responses.

Experimental:
Related substance A peak (area)—1,221
Sum of all relevant peaks (area)—180,543
1 × (1221/180,543) × 100% = 0.7% Related substance A

- **⟨731⟩ Loss on Drying (LOD)**

Percent Loss on Drying
Calculation:

$$\%\text{LOD} = \frac{[(W_D + W_U) - W_{D1}]}{W_U} \times 100\%$$

where
W_D = Weight of the bottle (g)
W_U = Weight of the sample (g)
W_{D1} = Weight of the dried sample and bottle (g)

Example:
Loss on drying ⟨731⟩: Dry it at 105° for 4 hours: it loses not more than 4.5% of its weight.

Experimental: 1.0293 g of sample was weighed into a 35.4688-g bottle. The dried sample and bottle weight after 4 hours at 105° was determined to be 36.4703 g.

$$\frac{[(35.4688\text{ g} + 1.0293\text{ g}) - 36.4703\text{ g}] \times 100\%}{1.0293\text{ g}} = 2.7\%\text{ LOD}$$

- **⟨733⟩ Loss on Ignition (LOI)**

Percent Loss on Ignition
Calculation:

$$\%\text{LOI} = \frac{[(W_D + W_U) - W_{D1}]}{W_U} \times 100\%$$

where
W_D = Weight of the crucible (g)
W_U = Weight of the sample (g)
W_{D1} = Weight of the ignited sample and crucible (g)

Example:
Loss on ignition ⟨733⟩: Transfer to a tared platinum crucible about 500 mg, weigh accurately, and ignite at 800 ± 25° to constant weight: it loses not more than 10.0% of its weight.

Experimental: 0.5023 g of sample was weighed into a 25.4688 g crucible. The ignited sample and crucible weight (at constant weight) was determined to be 25.9258 g.

$$\frac{[(25.4688\text{ g} + 0.5023\text{ g}) - 25.9258\text{ g}] \times 100\%}{0.5023\text{ g}} = 9.0\%\text{ LOI}$$

ATTACHMENT 2

Application of Calculations in General Chapters to Simplify and Clarify the Monographs

Example 1: Simplifying Monographs

USP Monograph (Active Sulfate): **Assay—**
Standard preparation—Dissolve an accurately weighed quantity of USP Active Non-sulfated RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.
Assay preparation—Transfer 60 mg of Active Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and 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 responses for the major peaks. Calculate the quantity, in mg, of Active Sulfate in the portion taken by the formula:

$$(115.98)C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Active Non-sulfated RS in the *Standard preparation,* and r_U and r_S are the Active Non-sulfated peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Revised *USP* Monograph (Active Sulfate): **Assay—**
Standard preparation—Dissolve an accurately weighed quantity of USP Active Non-sulfated RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.
Assay preparation—Transfer 60 mg of Active Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and 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 responses for the major peaks. Calculate the quantity, in mg, of Active Sulfate in the portion taken by *Formula 1,* (see *Chromatography* ⟨621⟩), where the correction factor, *F,* is equal to 1.1598 [NOTE: 1.1598 = Active Sulfate MW (711.87 g/mole)/Active Non-sulfated MW (613.80 g/mole)].

Example 2: Clarifying Monographs

Current *NF* Monograph (Aspartame): **Assay—**

Procedure—Transfer about 300 mg of Aspartame, accurately weighed, to a 150-mL beaker, dissolve in 1.5 mL of anhydrous formic acid, and add 60 mL of glacial acetic acid. Add crystal violet TS, and immediately titrate with *0.1 N Perchloric acid* to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of *0.1 N Perchloric acid* is equivalent to 29.43 mg of $C_{14}H_{18}N_2O_5$. [NOTE—A blank titration exceeding 0.1 mL may be due to excessive water content, and may cause loss of visual endpoint sensitivity.]

Revised *NF* Monograph (Aspartame): **Assay—**

Procedure—Transfer about 300 mg of Aspartame, accurately weighed, to a 150-mL beaker, dissolve in 1.5 mL of anhydrous formic acid, and add 60 mL of glacial acetic acid. Add crystal violet TS, and immediately titrate with *0.1 N Perchloric acid* to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of *0.1 N Perchloric acid* is equivalent to 29.43 mg of $C_{14}H_{18}N_2O_5$. Calculate the percentage of Aspartame in the portion of sample taken by *Formula 1* (see *Titrimetry* ⟨541⟩). [NOTE—A blank titration exceeding 0.1 mL may be due to excessive water content, and may cause loss of visual endpoint sensitivity.]

Comments on ''Compendial Calculations: Improving the Calculations in *USP–NF*''

USP Staff*

ABSTRACT This article briefly responds to and comments on ''Compendial Calculations: Improving the Calculations within *USP–NF*.''

USP staff shares the concerns expressed in ''Compendial Calculations: Improving the Calculations within *USP–NF*'' (*1*). In fact, USP staff published a *Stimuli* article earlier this year expressing similar concerns and additional ones and proposing some solutions (*2*). There is general agreement that the manner in which the formulas and other calculations expressed in current monographs is confusing and could potentially compromise a ''scientist's ability to understand and modify calculations where allowable revisions have been made.'' However, there are some practical issues in implementing the proposals in ''Compendial Calculations.''

1. The article primarily proposes that the formulas for techniques frequently used in *USP–NF* monographs, such as titration, chromatography, loss on drying, loss on ignition, etc., should be moved to the corresponding General Chapters with only the monograph-specific instructions and parameters included in monographs. However, the ''Current Status'' section of the article correctly recognizes that ''these calculations have become so specialized that they are monograph specific.'' This is precisely the reason why it would be inappropriate to move them to the corresponding General Chapters. It would be very confusing and unfriendly to force users to assemble an equation by combining two segments that are included in two different sections of *USP–NF*.

2. Most of the instructions and parameters included in monographs are monograph specific; therefore, this information has to be retained in each monograph. Thus, the potential space saving per monograph would be one to two lines—typically the line(s) in which the formula is presented. Given the complexity of having to look two places for a formula and the confusion that could follow the proposed change, USP staff believe it would not be appropriate to take such an approach. As mentioned in ''Compendial Calculations'' (*1*) and also in the article by Davani et al. (*2*), the current practice of combining several constants into one number is confusing. Davani et al. proposed keeping the formulas with individual monographs but breaking them down and including explanations for the constant and other terms in the formula. This is a significantly more user-friendly approach and will go a long way toward clarifying the formulas. Where appropriate, Davani et al. also proposed including critical intermediate steps in calculations rather than giving one final formula.

3. The ''Compendial Calculations'' article (*1*) indicated that because the calculations are monograph specific, they are not appropriate for a public standard. It is difficult to conceive having monographs but not having formulas or instructions for calculations in them.

4. The formulas proposed under the section *Chromatography* ⟨621⟩ depend on how the Relative Response Factor (RRF), *F,* or the Correction factor, is defined. The formulas proposed in this article are not universally accepted. Currently, *USP–NF* has several monographs in which RRF is used in the numerator, as proposed by this article, but about an equal number of monographs use RRF in the denominator. Thus, as mentioned above, such formulas are very monograph specific and should not be included in General Chapter ⟨621⟩ *Chromatography*. In addition, the proposal is not in accord with the recent effort by USP to standardize the use of this factor (*3*).

5. *USP–NF* currently has more than 4000 monographs, many of which would require revision, whichever approach is adopted. This is an extensive effort and would require significant staff and industry resources. Thus, USP proposes to take cautious steps in evaluating the proposals before committing to such an enormous task.

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REFERENCES

1. Travis P, Heck K, Teitz D, Virgili L, Wiggins M. Compendial Calculations: Improving the calculations within *USP–NF*. *Pharm Forum*. November–December 2005;31(6):1749–1755.
2. Davani B, Russo KA, Wilk A, Bhattacharyya L. Common pharmacopeial calculations in *USP* monographs. *Pharm Forum* March–April 2005;31(2):626–636.
3. Bhattacharyya L, Pappa H, Russo KA, Sheinin E, Williams RL. The use of relative response factors to determine impurities. *Pharm Forum*. May–June 2005;31(3):960–966.

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.

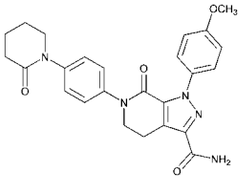
USP Dictionary of USAN and International Drug Names
2005 USP DICTIONARY SUPPLEMENT 4

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

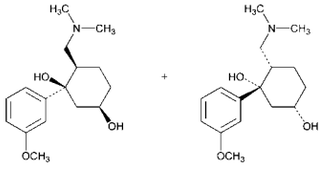
Newly Approved United States Adopted Names (USAN), Released for Publication

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.

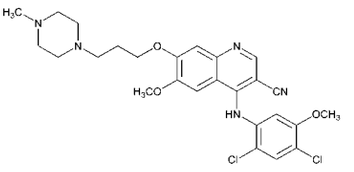
Apixaban [*2005*] (a pix′ a ban). $C_{25}H_{25}N_5O_4$. 459.50. (1) 1*H*-Pyrazolo[3,4-*c*]pyridine-3-carboxamide,4,5,6,7-tetrahydro-1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperidinyl)phenyl]-; (2) 1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. *CAS-503612-47-3*. *Anticoagulant, antithrombotic.* (Bristol-Myers Squibb) ✧*BMS-562247-01*



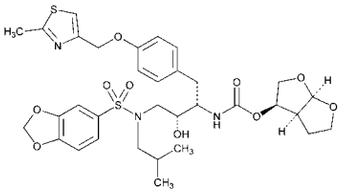
Axomadol [*2005*] (ax oh′ ma dole). $C_{16}H_{25}NO_3$. 279.40. (1) 1,3-Cyclohexanediol, 6-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1*R*,3*R*,6*R*)-*rel*-; (2) (1*RS*,3*RS*,6*RS*)-6-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexane-1,3-diol. *CAS-187219-99-4*. INN. *Treatment of pain, central analgesic.* (Gruñenthal GmbH, Germany) ✧*GRT151 base; BN110 base*



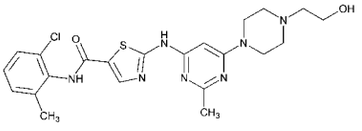
Bosutinib [*2005*] (boe sue′ ti nib). $C_{26}H_{29}Cl_2N_5O_3$. 530.50. (1) 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-; (2) 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile. *CAS-380843-75-4*. *Antineoplastic* (*Src kinase inhibitor*). (Wyeth) ✧*SKI-606*



Brecanavir [*2005*] (bre kan′ a veer). $C_{33}H_{41}N_3O_{10}S_2$. 703.80. (1) Carbamic acid, [(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(2-methylpropyl)amino]-2-hydroxy-1-[[4-[(2-methyl-4-thiazolyl)methoxy]phenyl]methyl]propyl]-, (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester; (2) (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl [(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(2-methylpropyl)amino]-2-hydroxy-1-[4-[(2-methylthiazol-4-yl)methoxy]benzyl]propyl]carbamate.*CAS-313682-08-5*. *Treatment of HIV infection in combination with other antiretroviral agents.* (GlaxoSmithKline) ✧*GW64085X*

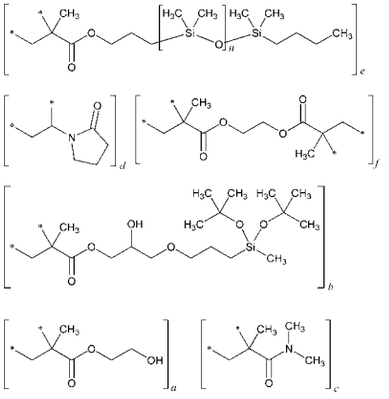


Dasatinib [*2005*] (da sa′ ti nib). $C_{22}H_{26}ClN_7O_2S$. 488.00. (1) 5-Thiazolecarboxamide-*N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-; (2) *N*-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]thiazole-5-carboxamide.*CAS-302962-49-8*. *Antineoplastic.* (Bristol-Myers Squibb) ✧*BMS-354825*



Denosumab [*2005*] (den oh sue′ mab). $C_{6404}H_{9912}N_{1724}O_{2004}S_{50}$. (1) Immunoglobulin G2, anti-(human osteoclast differentiation factor) (human monoclonal AMG162 heavy chain), disulfide with human monoclonal AMG162 light chain, dimer; (2) Immunoglobulin G2, anti-(human RANK ligand) (human monoclonal AMG162 heavy chain), disulfide with human monoclonal AMG162 light chain, dimer. Molecular weight is approximately 144,700 daltons. *CAS-615258-40-7. Prevention and treatment of all forms of osteoporosis or bone loss.* (Amgen) ✧*AMG 162*

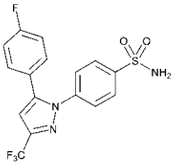
Galyfilcon A [*2002*] (gal ee fil′ kon). $(C_6H_{10}O_3)_a(C_{17}H_{38}O_6Si_3)_b(C_5H_9NO)_c(C_6H_9NO)_d(C_{35}H_{92}O_{13}Si_{12})_e(C_{10}H_{14}O_4)_f$. (1) Siloxanes and Silicones, di-Me, Bu group- and 3-[(2-methyl-1-oxo-2-propenyl)oxy]propyl group-terminated (n=11), polymers with *N,N*-dimethyl-2-propenamide, ethylene dimethacrylate, 2-hydroxyethyl methacrylate, 2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl methacrylate and vinylpyrrolidone; (2) Copolymer of 3-(23-butyltetracosamethyldodecasiloxanyl)propyl 2-methylprop-2-enoate (n=11), *N,N*-dimethylprop-2-enamide, 1-ethenylpyrrolidin-2-one, ethylene bis(2-methylprop-2-enoate), 2-hydroxyethyl 2-methylprop-2-enoate and (2*RS*)-2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl 2-methylprop-2-enoate. *CAS-446264-97-7. Contact lens material* (*hydrophilic*). (Vistakon) *[Note—The water content of the contact lens material is 47% at ambient temperature* ($23 \pm 2°C$)*, the purity of 2-hydroxyethyl methacrylate* (*HEMA*) *is 99%, and the oxygen permeability is* $60 \pm 2 \times 10^{-11}$ (cm^2/sec)($mL\ O_2/mL \times mm\ Hg$) *at 35°C* (*Dk value*)*.]*



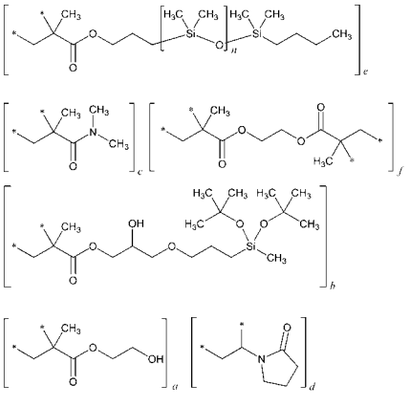
Hemoglobin Glutamer-200 (Bovine) [*1997*] (hee′ moe gloe bin glue ta mer). Hemoglobin-based oxygen carrier 301 is a solution of purified, glutaraldehyde-polymerized, bovine hemoglobin. The average polymer weight is 200,000 daltons. *CAS-192230-37-8. Oxygen carrier for veterinary use.* Oxyglobin Solution (Biopure) ✧*HBOC-301*

Hemoglobin Glutamer-250 (Bovine) [*1997*] (hee′ moe gloe bin glue ta mer). [Hemoglobin glutamer is INN.] Hemoglobin-based oxygen carrier 201 is a solution of purified, glutaraldehyde-polymerized, bovine hemoglobin. The average polymer weight is 250,000 daltons. *CAS-192230-36-7. Oxygen carrier and blood substitute for human use.* Hemopure (Biopure) ✧*HBOC-201*

Mavacoxib [*2005*] (may″ va kox′ ib). $C_{16}H_{11}F_4N_3O_2S$. 385.30. (1) Benzenesulfonamide, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]-; (2) 4-[5-(4-Fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide. *CAS-170569-88-7. Treatment of pain, inflammation, and fever.* (Pfizer) ✧*PHA 739,521*

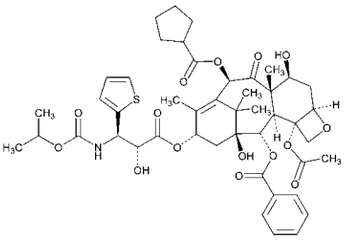


Senofilcon A [*2003*] (sen oh fil′ kon). $(C_6H_{10}O_3)_u(C_{17}H_{38}O_6Si_3)_v(C_5H_9NO)_w(C_6H_9NO)_x(C_{35}H_{92}O_{13}Si_{12})_y(C_{16}H_{26}O_7)_z$. (1) Siloxanes and silicones, di-Me, Bu group- and 3-[(2-methyl-1-oxo-2-propenyl)oxy]propyl group-terminated, polymers with *N,N*-dimethyl-2-propenamide, 2-hydroxyethyl methacrylate, 2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl methacrylate, tetraethylene glycol dimethacrylate and vinylpyrrolidone; (2) Copolymer of 3-(23-butyltetracosamethyldodecasiloxanyl)propyl 2-methylprop-2-enoate (n=11), *N,N*-dimethylprop-2-enamide, 1-ethenylpyrrolidin-2-one, 2-hydroxyethyl 2-methylprop-2-enoate, (2*RS*)-2-hydroxy-3-[3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]disiloxanyl]propoxy]propyl 2-methylprop-2-enoate and oxybis(ethyleneoxyethylene) bis(2-methylprop-2-enoate). *CAS-478799-92-7. Contact lens material* (*hydrophilic*). (Vistakon) *[Note—The water content of the contact lens material is 38% at ambient temperature* ($23 \pm 2°C$)*, and the oxygen permeability is* 103×10^{-11} (cm^2/sec)($mL\ O_2/mL \times$ mm Hg) *at 35°C* (*Dk value*)*.]*



Simotaxel [*2005*] (sim″ oh tax′ el). $C_{46}H_{57}NO_{15}S$. 896.00. (1) 2-Thiophenepropanoic acid, α-hydroxy-β-[[(1-methylethoxy)-carbonyl]amino]-, (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-12b-(acetyloxy)-12-(benzoyloxy)-6-[(cyclopentylcarbonyl)oxy]-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester, (α*R*,β*R*)-; (2) (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-4,11-Dihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxete-6,9,12,12b-tetrayl 12b-acetate 12-benzoate 6-cyclopentanecarboxylate 9-[(2*R*,3*R*)-2-hydroxy-3-[[(1-methylethoxy)carbonyl]amino]-3-(thiophen-2-yl)propanoate].

CAS-791635-59-1. *Second-line treatment of NSCLC and metastatic breast cancer.* (Wyeth) ✧*MST-997*



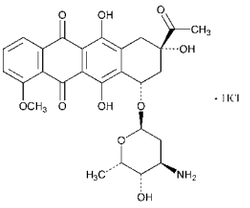
Nomenclature

Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

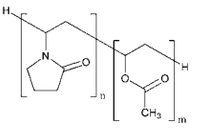
Epirubicin Hydrochloride

Change the chemical structure to read:



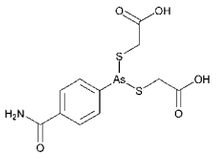
Copovidone

Change the chemical structure to read:



Thiacetarsamide

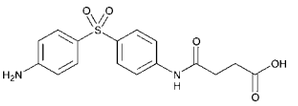
Change the chemical structure to read:



Succisulfone

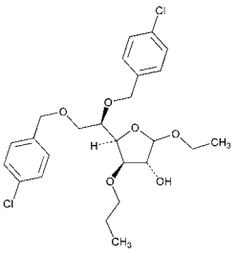
Change the molecular formula and chemical structure to read:

$C_{16}H_{16}N_2O_5S$



Clobenoside

Change the chemical structure to read:



Proposed International Nonproprietary Names

The following 53 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. 19, No. 2, 2005.

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
Antithrombin Alfa	*Anticoagulant*
Apixaban	*Anticoagulant*
Apratastat	*Antirheumatic (inhibition of TNF-α converting enzyme)*
Arasertaconazole	*Antifungal*
Avosentan	*Endothelin receptor antagonist*
Bapineuzumab	*Immunomodulator (amyloid β-peptide clearance enhancer)*
Belatacept	*Immunosuppressant*
Brivaracetam	*Nootropic agent*
Caricotamide	*Pharmaceutical adjuvant*
Catumaxomab	*Antineoplastic*
Dapiclermin	*Appetite suppressant*
Dexlansoprazole	*Anti-ulcer*
Dianicline	*Nicotinic acetylcholine receptor partial agonist*
Ecallantide	*Kallicrein inhibitor*
Ertumaxomab	*Antineoplastic*
Esmirtazapine	*Serotonin receptor antagonist*
Fosfluridine Tidoxil	*Antineoplastic*
Ispronicline	*Nicotinic acetylcholine receptor agonist*
Istaroxime	*Inotropic agent*
Lecozotan	*Serotonin 5-HT1a receptor antagonist*
Levolansoprazole	*Anti-ulcer*
Manitimus	*Immunosuppressant*
Mapatumumab	*Antineoplastic*
Nebicapone	*Antiparkinsonian*
Nerispirdine	*Na^+/K^+ channel blocker*
Ofatumumab	*Antineoplastic*
Olmesartan	*Angiotensine II receptor antagonist*
Padoporfin	*Photosensitizing agent*
Pagibaximab	*Immunomodulator*
Paliroden	*Nootropic agent*
Peforelin	*GnRH analogue with preferential FSH action*
Plerixafor	Blockade of chemokine (CXCR4) receptor
Plitidepsin	*Antineoplastic*
Pradefovir	*Antiviral*
Rimacalib	*Nonsteroidal anti-inflammatory*
Rivanicline	*Nicotinic acetylcholine receptor agonist*
Rivenprost	*Prostaglandin receptor agonist*
Satavaptan	*Vasopressin V_2 receptor antagonist*
Seletracetam	*Nootropic agent*
Sipoglitazar	*Antidiabetic*
Sunitinib	*Antineoplastic*
Surinabant	*CB1 cannabinoid receptor antagonist*
Tasidotin	*Antineoplastic*
Tasquinimod	*Immunomodulator*
Terutroban	*Tromboxane A_2 antagonist*
Tesetaxel	*Antineoplastic*
Tretazicar	*Antineoplastic*
Udenafil	*Vasodilator*
Valategrast	*Nonsteroidal anti-inflammatory*
Valopicitabine	*Antiviral*
Voloximab	*Antineoplastic*
Zabofloxacin	*Antibacterial*
Zalutumumab	*Antineoplastic*

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